Mast Therapeutics, Inc.
Form 10-K
March 26, 2014
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2013

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.)**
12390 El Camino Real, Suite 150, 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 x

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

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting

company in Rule 12b-2 of the Exchange Act.

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 28, 2013 was approximately $44.0 million based upon the closing price of the registrant s common stock on the NYSE MKT reported for such date. Shares of the registrant s common stock held by each officer and director of the registrant and by each person or entity who is known by the registrant to own beneficially 10% or more of the registrant s outstanding common stock have been excluded for purposes of the foregoing calculation on the basis that such persons and entities may be deemed to be affiliates of the registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 24, 2014, the registrant had 113,607,834 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 2014 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, 2013.

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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. Among the factors that could cause or contribute to material differences between our actual results and expectations indicated by the forward-looking statements are risks and uncertainties that 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, including MST-188; 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, including the active pharmaceutical ingredient and the finished drug product, 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 or 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 MST-188 or another 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 with respect to MST-188 and our MAST platform and AIR001; 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 these risks and uncertainties, 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

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PART I

Item 1. Business.

Overview

We are a 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, our lead product candidate. MST-188 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 damaged cell membranes. We recently acquired AIR001, an intermittently nebulized form of sodium nitrite that was being developed to treat pulmonary vascular disorders, and we are in the process of determining the optimal development strategy for this new asset.

We are enrolling subjects in EPIC (Evaluation of Purified 188 In Crisis), a pivotal phase 3 study of MST-188 in sickle cell disease. At the end of 2013, we had 40 study sites open in the U.S., putting us more than halfway toward our goal of opening approximately 70 EPIC sites in total, and we opened our first sites outside of the U.S. in the first quarter of 2014. MST-188 has orphan drug status for the treatment of sickle cell disease in the U.S. and European Union.

In 2013, we also advanced the development of MST-188 outside of sickle cell disease. We believe the pharmacologic effects of MST-188 support its development in more than one setting and we intend to develop MST-188 in multiple clinical indications, both independently and through collaborations. Our pipeline includes MST-188 development programs in adjunctive thrombolytic therapy (e.g., acute limb ischemia, stroke), heart failure, and resuscitation following major trauma (i.e., restoration of circulating blood volume and pressure). In March 2014, we initiated a phase 2, clinical proof-of-concept study of MST-188 in combination with recombinant tissue plasminogen activator, or rt-PA, in patients with acute lower limb ischemia to evaluate whether MST-188 improves the effectiveness of rt-PA therapy. We also plan to conduct a nonclinical study in an experimental model of thrombotic stroke to evaluate the potential for MST-188 to improve the therapeutic effect of tissue plasminogen activator and expand the window in which it is effective. With respect to our heart failure program, earlier this year, we announced positive results from a nonclinical model of chronic heart failure. Based in part on data from that study, we believe MST-188 may offer a new therapeutic approach for patients with heart failure. We plan to announce our clinical development strategy in heart failure later this year. During 2014, we also plan to evaluate MST-188 in a trauma model that may generate U.S. government interest in studying MST-188 as a resuscitation fluid following major trauma. In addition, we conduct other *ex vivo*, nonclinical *in vivo* and *in vitro* studies of MST-188 to further understand its pharmacologic effects and support our intellectual property positions.

In February 2014, we acquired Aires Pharmaceuticals, Inc., a privately-held Delaware corporation. Aires lead product candidate is AIR001 (sodium nitrite) inhalation solution and its development was focused on pulmonary hypertension (PH). Prior to the acquisition, Aires had been enrolling two phase 2 clinical studies of AIR001 in World Health Organization (WHO) Group 1 PH, or pulmonary arterial hypertension (PAH), but had terminated enrollment in those studies due to capital constraints and had begun the process of closing them. We expect data from the approximately 20 subjects who completed the protocol-specified 16 weeks of treatment in the third quarter of 2014. In addition, we are planning to support the expansion of an ongoing, university-sponsored, phase 2a clinical study of AIR001 to evaluate whether AIR001 may be effective in reducing pulmonary vascular resistance, pulmonary capillary wedge pressure and right atrial pressure while improving hemodynamic parameters, including right ventricular function, in patients with WHO Group 2 PH, or PH associated with left heart disease. In parallel, we are conferring with experts in

PH and heart disease to develop our clinical strategy for AIR001, which we expect to announce later this year.

In March 2013, we changed our name to Mast Therapeutics, Inc. to reflect the fundamental changes and restructuring that our company had undergone over the past several years, from the suspension of substantially all of business operations and just two employees in 2009 to a substantially new Board of Directors and management team, an influx of new capital, and the strategic refocus of our business in 2011 from reformulated chemotherapeutic programs to MST-188, an agent with potential to be a first-in-class therapy in multiple indications.

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We are a development-stage company and have not yet marketed or sold any products or generated any significant revenue.

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 in sickle cell disease. Enrolling subjects in our pivotal phase 3 study of MST-188 in vaso-occlusive crisis of sickle cell disease is one of our top priorities. Although predicting the rate of enrollment for EPIC is subject to a number of significant assumptions and the actual rate may differ materially, we expect to complete enrollment by the end of 2015. If study 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 this study. MST-188 has fast track designation with the FDA for the treatment of vaso-occlusive crisis of sickle cell disease.

Advance clinical development of MST-188 for use in combination with thrombolytics in complications of arterial disease. Thrombolytic agents, such as tissue plasminogen activator, or t-PA, are used to break up or dissolve blood clots, which are often the cause of acute complications, such as acute limb ischemia, stroke and heart attack. Data from experimental models and clinical studies demonstrate the potential for MST-188 to improve outcomes in patients experiencing complications resulting from atherosclerotic and thromboembolic processes. We believe that, based on the similar pathophysiology of atherosclerotic arterial disease (plaque-obstructed arteries reducing the flow of blood to tissue), an agent that is effective in one form of occlusive arterial disease, such as acute limb ischemia, or ALI, also may be effective in its other manifestations, such as thrombotic stroke. In March 2014, we initiated a phase 2, clinical proof-of-concept study in ALI that, if positive, not only would progress development of MST-188 in ALI, but also could generate interest in developing MST-188 in stroke. We anticipate that enrollment in the phase 2 study will take approximately 18 months. MST-188 has orphan drug designation for treatment of ALI in the U.S. and we plan to submit an application for orphan designation in the European Union during the second quarter of 2014.

Initiate clinical development of MST-188 in heart failure. We believe MST-188 may offer a new therapeutic approach for patients with heart failure. In contrast to current treatments, such as vasodilators and beta blockers, which can indirectly improve heart function, MST-188 s membrane sealant and hemorheologic activity may directly improve heart contractility and function. We previously announced that, in a randomized, placebo-controlled, nonclinical study in a model of chronic heart failure, a single, two-hour infusion of MST-188 demonstrated improved left ventricular systolic function that was significant immediately (at the end of MST-188 administration) and remained significant at one week, and, in some cases, at two weeks, after MST-188 administration. In addition, MST-188 resulted in statistically significant and progressive reductions in troponin-I and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), at both one week and two weeks after MST-188 administration. We are evaluating options for development of MST-188 in heart failure and plan to announce our clinical development strategy later this year.

Evaluate the potential of MST-188 in resuscitation following major trauma. The potential clinical benefits of MST-188 in resuscitation following major trauma (i.e., restoration of circulating blood volume and pressure) are suggested by the results of a variety of experimental models, including statistically significant improvements in survival. If the survival advantage observed in experimental models can be demonstrated in clinical studies, it would represent a multi-billion dollar opportunity and a significant benefit to both civilian and military populations. During 2013, we met with U.S. Department of Defense personnel to discuss potential collaborations in this area and, based on their feedback, in 2014, we plan to conduct a nonclinical study of MST-188 in an experimental model of trauma. The results of this study, if positive, may generate further interest in studying MST-188 as a resuscitation fluid following major trauma.

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Define clinical development strategy for AIR001. Prior to our acquisition of Aires in February 2014, clinical development of AIR001 was focused on pulmonary hypertension. Over the next few months, we will evaluate data from Aires terminated phase 2 studies in PAH and continue to consult with experts in pulmonary hypertension and heart failure to define the optimal clinical development strategy for AIR001. We also plan to support expansion of an ongoing phase 2a study sponsored by the University of Pittsburgh to evaluate whether AIR001 can reduce pulmonary vascular resistance, pulmonary capillary wedge pressure and right atrial pressure while improving hemodynamic parameters, including right ventricular function, in patients with WHO Group 2 PH. We plan to announce our clinical development strategy for AIR001 later this year.

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 purified and non-purified poloxamer 188, and over two decades of 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, MST-188.

The MAST platform provides us with several key benefits as we develop MST-188. In particular, we believe it:

Accelerates development of MST-188 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 MST-188 in healthy volunteers and our thorough QT/QTc study of MST-188 met its primary endpoint and demonstrated that, based on an analysis of electrocardiograms, MST-188 did not have an adverse effect on cardiac repolarization, as measured by the QT interval. Furthermore, we have successfully manufactured multiple batches of clinical trial material. As a result, we expect to move MST-188 directly into phase 2 studies and generate clinical proof-of-concept data in new indications in relatively short time frames with relatively modest investment. By leveraging already-completed pre-clinical and phase 1 clinical activities, 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 MST-188. We have filed for patent protection and continue to develop patent positions that we expect will provide exclusivity around the use of MST-188 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 MST-188 competitors. For example, unlike discrete small molecules, polymers (including the active ingredient in MST-188) 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 MST-188 in that 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 MST-188, without regard to indication.

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Increases partnering interest in and value of MST-188. We believe that we increase our ability to attract collaborators by pursuing multiple development programs within the MST-188 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 MST-188, regardless of the partnered indication, including through milestones, accelerating tiered royalties and, possibly, contingent value rights.

Reduces our overall risk profile. Pursuing multiple development programs reduces the risk associated with any one program, assuming MST-188 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 MST-188 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.

MST-188

We are leveraging the MAST platform to develop MST-188. MST-188 is formulated using a purified form of poloxamer 188. Substantial research has demonstrated that poloxamer 188, the active ingredient in MST-188, has cytoprotective and hemorheologic properties and inhibits inflammatory processes and thrombosis. As described below, purified poloxamer 188 was designed to preserve the activity but eliminate certain impurities and other substances that we believe were the cause of the acute renal dysfunction observed in clinical studies of non-purified poloxamer 188 conducted by a prior sponsor.

Composition and Hypothesized Mechanism of Action

The active ingredient in MST-188 is poloxamer 188, 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 MST-188 is not based on specific receptor/ligand binding interactions, which are the mechanistic bases for most drugs. Rather, its binding activity and pharmacologic effects are driven by hydrophobic adhesive interactions, driven in part by its hydrophobic core.

The cell membrane is comprised predominantly of lipids and proteins. The fundamental structure of the cell membrane is a phospholipid bilayer that forms a fluid, yet stable, selectively-permeable barrier between the aqueous environments of both the cell interior and exterior. The exterior surface of healthy cell membranes normally is hydrophilic, comprised of the polar head groups of lipid molecules that bury their hydrophobic tails in the interior of the bilayer. 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 result in increased 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.

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After intravenous administration, the MST-188 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. MST-188 does not bond covalently with the cell membrane and the adhesive interaction is reversible. If phospholipid density is restored, the physical adhesion may be reversed and MST-188 dislodges from the cell membrane and returns to circulation. While MST-188 adheres specifically to hydrophobic domains, these domains may be widespread in sick or injured patients. As a result, MST-188 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, MST-188 has demonstrated little or no affinity for hydrophilic domains and, thus, does not adhere to healthy cells.

Pharmacodynamics

MST-188 is believed to exert multiple pharmacologic effects as a result of its adhesion to hydrophobic domains. First, it protects cells by interrupting the pathological cascade associated with cell membrane dysfunction and the resulting 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.

Second, MST-188 improves blood flow, particularly in the microcirculation where the vast majority of oxygen and nutrient exchange occurs, thereby improving tissue perfusion (and reperfusion following ischemia). It impedes 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 anti-thrombotic/pro-fibrinolytic properties described below also contribute to improved blood flow.

Third, MST-188 inhibits 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, MST-188 helps prevent an inflammatory process from beginning.

Fourth, MST-188 helps 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 MST-188 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, MST-188 does not inhibit strong platelet-activation stimuli (e.g., platelet/receptor interactions directly at the endothelium). Accordingly, we believe MST-188 does not negatively affect normal hemostatic function, which is supported by data from multiple nonclinical studies. Further, MST-188 facilitates fibrinolysis, the body s natural process of dissolving a thrombus. MST-188 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 MST-188 (cytoprotective, hemorheologic, anti-thrombotic/pro-fibrinolytic, anti-inflammatory) 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.

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The potential clinical benefit of MST-188 is greatest in diseases where improving microcirculatory insufficiency is central to improving clinical outcomes. This includes a wide range of seemingly unrelated diseases and conditions. Poloxamer 188 has shown effectiveness in experimental models of stroke, heart failure, 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 Hypothesized Mechanism of Action, MST-188 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 poloxamer backbone are not susceptible to biologically relevant metabolic pathways in humans. 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 metabolization 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, poloxamer 188 was generally well-tolerated, with the exception of renal toxicities associated with the non-purified form of poloxamer 188; in particular, in a 2,950-patient, randomized, controlled study in acute myocardial infarction conducted by Burroughs Wellcome (now, GlaxoSmithKline), which we refer to as the CORE study. In contrast, as discussed below, no clinically significant elevations in serum creatinine have been observed in patients treated with purified poloxamer 188.

In July 2013, we announced results of our thorough QT/QTc clinical study of MST-188, or the TQT study. The study met its primary endpoint and demonstrated that, based on analysis of electrocardiograms, MST-188 did not have an adverse effect on cardiac repolarization, as measured by prolongation of the QT interval. Sixty four healthy volunteers received MST-188 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 MST-188 on the QT/QTc intervals.

Purified Poloxamer 188

The therapeutic potential of non-purified poloxamer 188 is limited by toxicities associated with low molecular weight substances (e.g., di-block polymers, oligomers, gycols, aldehydes) 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 prior clinical studies of non-purified poloxamer 188, including the CORE study, and are a principal reason why clinical development of non-purified poloxamer 188 was discontinued by Burroughs Wellcome.

To address the renal toxicity associated with non-purified poloxamer 188, a proprietary manufacturing and purification process was developed to remove certain low molecular weight substances present in non-purified poloxamer 188. In nonclinical studies, compared to the non-purified version, purified poloxamer 188 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. In addition, no difference was observed in the efficacy of purified poloxamer 188 compared to non-purified poloxamer 188.

In the seven clinical studies of purified poloxamer 188 completed to date, including a 255-patient, phase 3 study in sickle cell disease, purified poloxamer 188 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 non-purified poloxamer 188, no clinically significant elevations in serum creatinine were observed in patients treated with purified poloxamer 188. The active pharmaceutical ingredient in MST-188 is purified poloxamer 188. In March 2014, we announced that the United States Adopted Names Council had selected vepoloxamer as the unique, non-proprietary (generic) name for the API in MST-188, which we had sought to clearly identify it from non-purified poloxamers. In support of our application, we submitted that drug products containing non-purified poloxamers should not be substituted for MST-188 and that confusion between the two could have serious toxicity consequences.

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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. More than $1.0 billion is spent annually in the U.S. to treat patients with sickle cell disease.

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 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

We estimate that, in the U.S., sickle cell disease results in approximately 100,000 hospitalizations 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 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 currently available therapeutic agents with demonstrated efficacy in 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, MST-188 has the potential to reduce the severity and shorten the duration of vaso-occlusive crisis and improve patient outcomes.

Clinical Development

Overview

MST-188 currently is being evaluated in a phase 3 study in sickle cell disease. In prior-sponsor clinical studies, MST-188 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, MST-188 was generally well-tolerated. Based on an integrated analysis of all four 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 MST-188 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.

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Ongoing and Planned Clinical Studies

Phase 3 Study; Evaluation of Purified 188 In Crisis (EPIC). In May 2013, we began enrolling subjects in EPIC, a randomized, double-blind, two-arm, placebo-controlled, phase 3 study of MST-188 in patients with sickle cell disease. The primary objective is to demonstrate that MST-188 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 as little as a 16-hour difference between treatment arms and 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 40 sites in the U.S. and approximately 30 sites outside the U.S. By the end of 2013, we had opened 40 sites in the U.S. and overall study enrollment for the first six months was consistent with internal projections. In the first quarter of 2014, we opened our first clinical sites outside of the U.S. and we expect to have approximately 25 sites open in foreign jurisdictions by the end of 2014. 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 by the end of 2015.

EPIC Sub-Study. It is generally believed that the long-term morbidity and 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. MST-188 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. In a sub-study within EPIC, we plan to investigate and quantify the effect of MST-188 on microvascular blood flow, indirectly measured by tissue oxygenation using a non-invasive method, and evaluate the relationship between tissue oxygenation and clinical outcomes, such as the duration of vaso-occlusive crisis. Approximately 30 patients who are concurrently randomized in EPIC will be enrolled in this sub-study. We submitted the protocol for the sub-study to the FDA in 2013 and plan to initiate it during the second quarter of 2014.

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 MST-188 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 MST-188 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 MST-188 group compared to the placebo group (p=0.010).

A potentially significant limitation of Study C97-1248 is that it did not follow subjects until hospital discharge; 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 the MST-188 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 MST-188 achieved crisis resolution within 168 hours, compared to 37% in the control group (p=0.02). Likewise, in the under-16 age group, over 60% of the MST-188 group achieved crisis resolution within 168 hours, compared to under 28% of the control group (p=0.009).

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Notably, 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 fewer than the originally-planned number of patients, which was 350 patients, may have further diluted the treatment effect observed in the study, or 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; 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 MST-188 and placebo groups. Notably, there were no clinically significant changes in renal function following treatment with MST-188 compared to placebo. The MST-188 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 MST-188 group compared to the placebo group and their incidences for MST-188 and placebo patients, 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 MST-188 and placebo groups, respectively. Six patients in the MST-188 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 MST-188 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 MST-188.

Phase 1 Study in Vaso-Occlusive Crisis (Study C96-1237). A phase 1, multicenter study was conducted to evaluate the safety and pharmacokinetics of MST-188 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 study drug. The serious adverse events experienced by the sixth patient were nausea, vomiting, and abdominal pain that were considered possibly related to study drug. 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 MST-188 in patients with sickle cell disease experiencing vaso-occlusive crisis. The study enrolled 28 patients, 16 of whom were children (ages 18 and younger). MST-188 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.

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Acute Chest Syndrome (Study C97-1243). A dose-escalating, multicenter study was conducted to evaluate the safety and pharmacokinetics of MST-188 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 MST-188 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, MST-188 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 Non-Purified P188 in Vaso-Occlusive Crisis (Study 005). Prior to development of purified poloxamer 188, non-purified poloxamer 188 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 non-purified 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 non-purified poloxamer 188 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 non-purified poloxamer 188 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 non-purified poloxamer 188 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 non-purified poloxamer 188 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, non-purified 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 non-purified 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.

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Arterial Disease MST-188 as Adjunctive Therapy to Thrombolytics for Acute Complications

Introduction

As discussed more fully below, data from experimental models and clinical studies demonstrate the potential of MST-188 to improve outcomes in patients experiencing complications of arterial disease. For these indications, we believe MST-188 may be useful as a stand-alone agent or as an adjunct to thrombolytics. We plan first to demonstrate 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 clinical data generated in ALI studies to find a partner to develop MST-188 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 18,000 hospital admissions for ALI in 2011, and the in-hospital mortality rate has not changed significantly since the late 1990s. Only 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.

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Recombinant tissue plasminogen activator (rt-PA) is FDA-approved and indicated for the management of acute myocardial infarction, acute ischemic stroke and acute pulmonary embolism. No thrombolytics, including rt-PA, 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 rt-PA 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. 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 less risk of bleeding complications represent 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 and over 85% of all strokes are ischemic strokes. Treatment options for 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, rt-PA 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, rt-PA 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. We believe the mechanistic activities of MST-188, which facilitate thrombolysis and inhibit reperfusion injury and re-occlusion, have potential to increase the speed of thrombolysis. In addition, MST-188 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

MST-188 s utility as an adjunct to thrombolytics has been demonstrated in experimental studies, as discussed below.

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% shorter 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.

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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 complete 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

Clinical trials directly evaluating the effect of MST-188 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 in patients with acute myocardial infarction and sickle cell disease. We believe these previously observed effects have potential to translate into clinically meaningful benefits in ALI, stroke and other conditions where thrombolytics are indicated or useful.

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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, seventy one patients with symptoms consistent with acute myocardial infarction were randomized shortly after initiating thrombolytic therapy to receive poloxamer 188 (test) 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 Purified Poloxamer 188. 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.

The effect of MST-188 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 MST-188 on real-time microcirculation in the bulbar conjunctiva during vaso-occlusive crisis. Subjects were randomly assigned to receive MST-188 (test) or placebo (control). Following treatment, compared to control, all four patients treated with MST-188 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. For the MST-188 subjects, the velocity values observed at seven hours after initiation of treatment were similar to historical steady-state (non-crisis) values for sickle cell patients.

Planned Development

Acute Limb Ischemia

In March 2014, we initiated a phase 2, randomized, double-blind, placebo-controlled, multi-center, clinical proof-of-concept study to evaluate the safety and efficacy of MST-188 in combination with rt-PA in patients with

ALI. The study will enroll approximately 60 patients with Rutherford Category IIa and IIb acute lower limb ischemia receiving catheter-directed rt-PA and compare a high dose and low dose of MST-188 against rt-PA alone. We plan to conduct the study at approximately 15 sites within and outside the U.S. The primary objectives of the study will be to evaluate the safety and efficacy of MST-188 in combination with rt-PA and whether MST-188 results in more rapid thrombolysis and tissue perfusion. The secondary objectives will be to assess the clinically-meaningful benefit of MST-188 in combination with rt-PA 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 the study will take approximately 18 months to enroll.

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Thrombotic Stroke

Although we currently are focused on ALI, there may be substantial growth opportunities for MST-188 within arterial disease, such as stroke. We believe that, based on the similar pathophysiology of atherosclerotic arterial disease (plaque-obstructed arteries reducing the flow of blood to tissue), an agent that is effective in one form of occlusive arterial disease also may be effective in its other manifestations. Our strategy in arterial disease is first to demonstrate the utility of MST-188 in patients with ALI, where we believe the potential to demonstrate a treatment effect is greatest. However, in parallel, we plan to conduct a nonclinical study in an experimental model of thrombotic stroke to evaluate MST-188 s potential to improve the therapeutic effect of rt-PA and expand the window in which it is effective and we expect to initiate that study during the second quarter of 2014. If, in a nonclinical model, MST-188 increases the therapeutic benefits of rt-PA, and, if our phase 2 clinical study in ALI demonstrates that MST-188 accelerates time-to-reperfusion, we believe there will be interest from potential partners to develop MST-188 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. Decompensation, or acute decompensation, describes the condition when these compensatory mechanisms 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 s 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.

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MST-188 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. MST-188 s membrane-sealing activity may help restore weakened cardiac cell membranes, thus minimizing calcium overload injury and directly improving heart contractility and function. MST-188 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 MST-188 can alter the trajectory of heart failure as a result of decompensation, 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 Study

To investigate the utility of MST-188 as a treatment for heart failure, we conducted a randomized, placebo-controlled, nonclinical study of MST-188 in a well-established experimental model of chronic heart failure. A single dose of MST-188 (low or high dose) or placebo was administered 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, a Michigan non-profit corporation. 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 MST-188 improved left ventricular systolic function that was significant immediately (at the end of MST-188 administration) and remained significant at one week (and, in some cases, at two weeks) after MST-188 administration. In particular, MST-188 demonstrated a statistically significant improvement in left ventricular ejection fraction, end-systolic volume, stroke volume and cardiac output.

In addition, MST-188 resulted in statistically significant and progressive reductions in troponin-I, at both one week and two weeks after MST-188 administration. Specifically, at two weeks post-administration, compared to baseline values, mean reduction (improvement) in troponin was 46.7% for low-dose MST-188 and 48.8% for high-dose MST-188. 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 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.

MST-188 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 MST-188 administration. Specifically, at two weeks post-administration, compared to baseline values, mean reduction (improvement) in NT-proBNP was 54.5% for low-dose MST-188 and 61.4% for high-dose MST-188. 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 study found that higher NT-proBNP levels are associated with increased 180-day all-cause mortality.

Based on these data, we believe MST-188 may provide a novel mechanistic approach to the treatment of heart failure. Importantly, data from this nonclinical study are consistent with prior studies showing MST-188 directly improved

cardiac function without increasing cardiac energy requirements, a critical requirement for any new therapeutic designed to directly improve a failing heart.

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Planned Development

Since we announced the data from our nonclinical proof-of-concept study in January 2014, we have met with, and we continue to meet with, experts in heart failure to discuss the results and various development strategies for MST-188 in heart failure. With their input, we are formulating a clinical development plan in this indication. We expect to submit an IND covering the use of MST-188 in heart failure to FDA in the summer of 2014. If FDA feedback is positive, we expect to initiate a phase 2, dose-finding, clinical study of MST-188 in patients with heart failure in the first half of 2015. However, FDA may have questions regarding our clinical development plans or request additional information that alters our plans and/or delays expected timing. Even if FDA feedback is positive, we may elect to delay initiation of clinical studies as we finalize manufacturing-related activities that we believe will enhance our proprietary position around MST-188. While we do not believe that contemplated changes will require additional preclinical activities, FDA may request or require such activities prior to initiating clinical studies.

Resuscitation Following Major Trauma

Introduction

As discussed more fully below, MST-188 has improved survival in numerous nonclinical studies in hemorrhagic shock, and we believe it has potential as a resuscitation fluid to improve outcomes for patients who experience shock following major trauma. However, based on our current focus on sickle cell disease, acute limb ischemia and heart failure, it is unlikely we would initiate a clinical study in this indication without funding from the U.S. government or some other third-party collaborator.

Overview

Trauma care is a major part of the U.S. medical economic system. Based on 2009 data, trauma-related disorders rank among the top five most costly medical conditions in the U.S., with estimated health care expenditures totaling more than $80 billion, and we estimate that the incidence of severe hemorrhage resulting from trauma is greater than 780,000 per year. Major trauma typically involves multiple injuries, blood loss, shock, need for emergency surgical intervention and resuscitation.

Shock following massive bleeding, or hemorrhagic shock, is a physiologic response based on an imbalance between systemic oxygen delivery and oxygen consumption. Initially, as circulating blood volume falls due to hemorrhage, the body activates a variety of physiologic responses to maintain blood pressure and the flow of oxygen-rich blood to tissues. However, if circulating volume is not restored, these compensatory mechanisms begin to fail. As cells become increasingly hypoxic and their metabolic energy requirements are not met, cell membrane integrity is compromised, ions diffuse between the intracellular and extracellular environments, fluid leaks into the interstitial space and inflammatory and clotting cascades are triggered. Even following resolution of the underlying hemorrhage and restoration of circulating volume, periods of ischemia can result in tissue and organ damage and death.

The primary treatment goal in major trauma is to stop the bleeding, typically through surgery, followed by restoration of circulating blood volume and pressure, referred to as resuscitation. Resuscitation is achieved through intravenous administration of blood products (e.g., packed red blood cells, plasma) and non-blood fluids (e.g., colloids, crystalloids), as well as with the use of vasopressors to constrict blood vessels and increase blood pressure.

Significant Unmet Need

Since World War I, the epidemiology of death from trauma has changed. Rates of early hospital death from blood loss have been reduced with the introduction of damage control surgery. The advent of regional trauma systems that enable rapid triage and intervention has improved mortality rates. However, while victims of major trauma often will survive, complications are frequent and recovery prolonged. Treatment costs are high and increase rapidly with severity. The estimated per patient cost to treat trauma-induced shock is $51,000, rising to $148,000 in cases of severe shock and $312,000 if multiple organ failure presents.

Multiple organ failure, or MOF, remains a major cause of prolonged stay in the intensive care unit, or ICU. Increased understanding of the pathogenesis of MOF suggests that shock initiates a dysfunctional inflammatory process that causes or contributes to MOF. While resuscitation is necessary for patient survival, most resuscitation fluids are not directed at modulating inflammation and, in fact, may worsen it. Reperfusion injury, where tissue and organ damage occur due to the introduction of blood and other resuscitation fluids (e.g., as a result of oxidative damage and inflammation), remains a significant concern.

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Despite significant morbidity and expense, for over 20 years, there have been no major advances in therapeutics approved for resuscitation following severe hemorrhage. Based on its hemorheologic, cytoprotective and anti-inflammatory properties, MST-188 may have utility as an adjunct therapy for resuscitation following major trauma.

Nonclinical Data

The potential clinical benefits of MST-188 are suggested by the results of numerous experimental models of hemorrhagic shock. For example, an article in *Shock* (October 2009) summarized the results of MST-188 in multiple models of hemorrhagic shock. In these studies, which we refer to as the Hunter Studies, relative to control, MST-188 decreased fluid requirements required to regain and maintain hemodynamic performance goals ($p = 0.0002$); reduced tissue permeability/fluid extravasation in the lung and small intestine ($p<0.01$); reduced myeloperoxidase, a marker of inflammation ($p=0.02$), and caspases 3, 6, 8 and 9, mediators of apoptosis ($p=0.04$); and improved survival ($p<0.001$). The study investigators concluded that MST-188 has a significant cytoprotective effect in preventing endothelial and other cell damage during hypotension and reperfusion and inhibited both necrosis and apoptosis induced by trauma.

A study published in *Resuscitation* (June 2011) and funded by the Defense Advanced Research Projects Agency (DARPA) Surviving Blood Loss (SBL) program, which we refer to as the DARPA Study, evaluated MST-188 in a severe hemorrhage model developed specifically for evaluating low volume resuscitation products as part of the DARPA SBL program. MST-188 significantly improved median survival time after severe controlled hemorrhage, compared to control ($p=0.0186$). The DARPA Study also evaluated thrombelastography, or TEG, a measure of the efficiency of blood coagulation. Results from the DARPA Study suggested that MST-188 caused TEG abnormalities consistent with an anti-coagulant effect. Thus, while the survival results were positive and consistent with prior studies, the study investigators were uncertain as to the utility of MST-188 in uncontrolled hemorrhage due to its potentially negative effect on coagulation, based on the TEG results, and recommended additional experiments to determine the physiological significance of the TEG results.

Planned Development and Other Activities

In 2013, we met with personnel from the U.S. Department of Defense to discuss potential collaboration for development of MST-188 as a resuscitation fluid following major trauma. Based on feedback from that meeting, during the second half of 2014, we plan to conduct a nonclinical study of MST-188 in an experimental model of trauma to evaluate whether MST-188 adversely affects hemostasis following trauma, among other things. If the results are positive, the U.S. government may have renewed interest in developing MST-188 as a therapy in major trauma.

AIR001

Pursuant to an agreement and plan of merger, in February 2014, Aires Pharmaceuticals, Inc., formerly a privately-held Delaware corporation, became a wholly-owned subsidiary of ours. Aires lead product candidate is AIR001 (sodium nitrite) inhalation solution. AIR001, also known as Aironite®, is an 80 mg/mL solution of sodium nitrite in a sterile phosphate buffer solution for nebulization. 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. Nitrite mediated NO formation has been shown to have multiple vasoprotective characteristics, including inhibition of endothelial cell apoptosis, inhibition of platelet aggregation and adhesion, inhibition of leukocyte chemotaxis, and inhibition of smooth muscle cell proliferation and migration. Results of nitrite use in monocrotoline and hypoxic animal models of pulmonary hypertension have demonstrated improved remodeling both in the pulmonary vasculature and right ventricle. In addition, recent nonclinical studies

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.

Prior to the acquisition, clinical development of AIR001 had been focused primarily on WHO Group 1 pulmonary hypertension (PH), or pulmonary arterial hypertension (PAH), a progressive, life-threatening disorder characterized by abnormally high blood pressure (hypertension) in the pulmonary arteries, the blood vessels that carry blood from the heart to the lungs. The increased pressure occurs when the small arteries of the lung become abnormally narrow in diameter, increasing the resistance to blood flow through the lungs, which strains the right ventricle of the heart as it tries to pump blood through the narrowed arteries. Although pharmaceutical treatments can control symptoms of PAH, which include shortness of breath, excessive fatigue, dizziness and fainting, none are curative and cardiac performance diminishes over time resulting in heart failure and death. AIR001 has orphan designation status in the U.S. and European Union for the treatment of PAH. Aires had been enrolling two phase 2 studies of AIR001 in PAH. However, before entering into the merger agreement with us, due to capital constraints, Aires had terminated enrollment and had begun the process of closing those studies. Currently, Aires is continuing the closing process for those studies. Though the PAH studies did not complete enrollment, we expect data from patients who completed the protocol-specified 16 weeks of treatment (approximately 20 subjects) in the third quarter of 2014.

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Over the next several months we will analyze data from the phase 2 PAH studies and continue to meet with clinical and regulatory experts in PH and heart failure to determine the optimal development strategy for AIR001, which we expect to announce later this year. We plan to support the expansion of an ongoing, phase 2a study of AIR001 sponsored by the University of Pittsburgh to evaluate whether AIR001 can reduce pulmonary vascular resistance, pulmonary capillary wedge pressure and right arterial pressure while improving hemodynamic parameters, including right ventricular function, in patients with PH associated with heart failure (WHO Group 2 PH). That study currently is evaluating whether AIR001 can improve hemodynamics in patients with WHO Group 1 and WHO Group 3 PH. Data from the study could be available as early as summer 2015. In addition, we are aware of other planned investigator-sponsored clinical studies of AIR001 in WHO Group 2 PH patients and we may determine to provide some level of support to those studies, the data from which could help inform our development strategy.

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.

For MST-188 clinical trial material, we have entered into supply agreements with Pierre Fabre Médicament (PFM) and Patheon Inc. for API 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 MST-188. We have begun to evaluate other vendors, but discussions are at an early stage. Therefore, if PFM or Patheon become unable or unwilling to perform, we could experience protracted delays or interruptions in the supply of clinical trial material, particularly as our clinical trial material needs increase as we conduct additional studies of MST-188. Our current agreements with PFM and Patheon may not cover all of our clinical trial material needs and we may meet future clinical trial material needs through 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 and initiation of new studies. As development of MST-188 progresses, we plan to pursue agreements for commercial production of MST-188. In the event negotiations are protracted or unsuccessful, commercialization of MST-188, if it receives regulatory approval, may be delayed.

In addition, although commercially available, there are a limited number of sources of poloxamer 188, the API starting material for MST-188. BASF, the current supplier of the API 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 including those involving proprietary API starting material, alternative purification processes, unique analytical methods and new drug product formulations. However, discussions with potential manufacturers and suppliers are at an early stage. While we do not believe that the contemplated changes will require additional preclinical activities, we have not yet discussed these potential changes with regulatory authorities.

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 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.

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Intellectual Property

Our commercial success depends in large 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.

For particular indications, such as rare or orphan diseases, our products may benefit from periods of post-approval marketing exclusivity. MST-188 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 seek orphan designation for MST-188 for the treatment of acute limb ischemia in the European Union during the second quarter of 2014. AIR001 has orphan drug status in the U.S. and European Union for the treatment of pulmonary arterial hypertension. As described below under Government Regulation Orphan Drug Designation, for example, if MST-188 is the first drug product in which poloxamer 188 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 poloxamer 188 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. With regard to the European Union, MST-188 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 or AIR001 is approved.

Since we acquired MST-188 in 2011, we have filed for patent protection covering our proprietary supercritical fluid extraction process, methods of using poloxamers in various clinical settings, and the use of poloxamers in combination therapy. We continue to evaluate new patent concepts and plan to file additional patent applications. In particular, we are developing a patent position around the use and optimal dosing of MST-188, and we expect to use data from the EPIC study.

In addition to patent protection related to our poloxamer purification process, we continue to expand our proprietary manufacturing know-how. For macromolecules, such as MST-188, 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 products that are equivalent to MST-188 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 MST-188.

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.

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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.

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 MST-188, which has potential application in a wide range of serious or life-threatening diseases and conditions characterized by microcirculatory insufficiency, and we recently acquired the AIR001 program, development of which has been focused in pulmonary hypertension. 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, ALI, and other indications we may pursue. Legislative action may generate further interest.

MST-188 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, 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 or cure sickle cell disease and 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 privately-held companies, GlycoMimetics, Inc. and Selexys Pharmaceuticals Corporation, respectively, with clinical-stage agents for the treatment of vaso-occlusive crisis. In January 2014, GlycoMimetics announced that it expects Pfizer to initiate a phase 3 clinical study of GMI-1070 in adult and pediatric patients in the second half of 2014, pending approval through Pfizer s governance process. 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. Further, in March 2014, Emmaus Life Sciences, Inc. disclosed that top-line data from its phase 3 clinical study of L-glutamine in sickle cell disease showed a statistically significant reduction in the frequency of sickle cell crisis and announced its plans to submit an NDA in mid-2014 for marketing approval of L-glutamine to treat patients with sickle cell disease. Additionally, 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.

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More broadly, MST-188 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.

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 MST-188 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 rt-PA is slow and major hemorrhagic complications are frequent. In stroke patients, due to bleeding risks associated with rt-PA, rt-PA 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 MST-188, 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 MST-188 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, MST-188 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 MST-188, they may become entrenched in the standard of care, diminish the need for MST-188, 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, 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.

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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 completed a large, phase 3 study of RLX030 (serelaxin), a relaxin receptor agonist, in patients with acute heart failure and is enrolling subjects in a second, 6,000-patient phase 3 study of RLX030. Novartis has submitted applications for approval of RLX030 to numerous health authorities, including the FDA, which has granted RLX030 breakthrough therapy designation, and the European Medicines Agency. Novartis also is developing LCZ696, an angiotensin receptor neprilysin inhibitor, and has initiated two phase 3 studies to study its efficacy and safety as a treatment for chronic heart failure. 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, MST-188 could compete with one or more of these therapies. Should any of these other investigational therapies receive approval prior to MST-188, they may become entrenched in the standard of care, diminish the need for MST-188, or be difficult to displace.

Resuscitation Following Major Trauma

We are aware of various organizations that are developing therapies for hemorrhagic shock, including agents to improve blood flow in the microvasculature, improve oxygenation of ischemic tissues, and/or prevent reperfusion injury. Some of these organizations have received funding from the federal government to progress their research and development in this area. Efforts to improve patient outcomes after surgery for severe hemorrhage include new types and methods of fluid resuscitation (e.g., anti-platelet, hormonal, and hypertonic agents, pressors, and blood factors, additives or substitutes). To the extent other therapies demonstrate acceptable safety and efficacy and receive regulatory approval prior to MST-188, the need for MST-188 may be diminished. In addition to investigational pharmacologic approaches, new resuscitation protocols are being explored to reduce morbidity and mortality following major hemorrhage and, to the extent they are successful, they may diminish the need for MST-188, should it be approved.

AIR001 Program

We are evaluating our development strategy for AIR001, which includes assessment of the competitive landscapes in indications for which we believe AIR001 may demonstrate clinical benefit. In general, there is significant competition in treatment of pulmonary vascular disorders, and we expect AIR001, if approved, will face significant competition in the marketplace. However, we are not aware of any treatments of proven benefit for patients with PH associated with heart failure (WHO Group 2).

Acquisition of SynthRx, Inc.

During 2010 and the first half of 2011, our business strategy involved a particular focus on expanding our product pipeline. We retained an investment banking firm to advise us in this regard and our board of directors formed a special committee to assist it in evaluating potential opportunities. Our management and the special committee, with assistance from the investment bank and other consultants, evaluated numerous opportunities with companies with a wide range of development programs. During this process, we identified SynthRx, Inc. as a company whose lead product candidate, which we are now developing as MST-188, was a strong fit with our pipeline expansion strategy. SynthRx was a private company formed in 2004 to acquire purified poloxamer 188 from CytRx Corporation, but after acquiring rights to purified poloxamer 188, SynthRx did not have the financial resources to pursue its development. The co-founders of SynthRx had been involved with the development of poloxamer 188 and purified poloxamer 188 as employees of CytRx.

In April 2011, we completed the acquisition of SynthRx, Inc. pursuant to an agreement and plan of merger, and SynthRx became a wholly owned subsidiary of ours. The payment terms of the merger agreement were structured such that the majority of the merger consideration would be payable only in the event of achievement of the milestones set forth in the merger agreement. All of the merger consideration was intended to be paid in shares of our common stock and, in June 2011 at our annual meeting of stockholders, our stockholders approved the issuance of shares of our common stock, in lieu of any cash payments, in accordance with the terms of the merger agreement. As of March 24, 2014, there are outstanding an aggregate of 1,596,772 shares of our common stock that we issued to the former SynthRx stockholders. An aggregate of 2,800,851 shares were issued upon the closing of the merger, but we repurchased 1,454,079 of those shares in December 2012 for $0.001 per share pursuant to the exercise of a repurchase right triggered as a result of the timing of and planned number of subjects in the EPIC study. 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 MST-188 achieves certain milestones, with 3,839,400 shares issuable upon the FDA s acceptance for review of a NDA covering the use of purified poloxamer 188 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.

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Under the terms of the merger agreement, we also agreed, among other things, (a) to use commercially reasonable efforts until the earlier of achievement of the Third Milestone, which is approval of an NDA covering the use of purified poloxamer 188 for the treatment of sickle cell crisis in children, or February 12, 2015 to develop an intravenous injection product in which purified poloxamer 188 is an active ingredient; and (b) until the earlier of the achievement of the Third Milestone and February 12, 2015, not to consummate a change of control with a third party that involves all or substantially all of SynthRx s assets, except (i) in connection with an Exempt Transaction (as described below) or (ii) with the written consent of SynthRx, which consent shall not be unreasonably withheld, conditioned or delayed. Under the merger agreement, an Exempt Transaction is a change of control that closes prior to achievement of the Third Milestone in which the acquiror agrees in writing to submit an NDA covering the use of purified poloxamer 188 for the treatment of sickle cell crisis in children, or the 188 NDA, for FDA approval (or, if there are unexpected safety or regulatory issues, to conduct activities to address or resolve such issues) until the earlier of (x) the date that, beginning on April 8, 2011 and thereafter, the aggregate expenditure related to the program involving the product candidate on which the 188 NDA is to be based is at least $15.0 million and (y) April 8, 2015; provided, however, such acquiror shall be relieved of such obligations under certain specified conditions.

Acquisition of Aires Pharmaceuticals

In February 2014, we completed the acquisition of Aires Pharmaceuticals, Inc. pursuant to an agreement and plan of merger, and Aires became a wholly owned subsidiary of ours. Aires lead product candidate, AIR001 (sodium nitrite) inhalation solution, is being developed to treat pulmonary vascular disorders. Prior to the acquisition, development of AIR001 was focused in pulmonary arterial hypertension.

Pursuant to the terms of the merger agreement, all outstanding shares of Aires capital stock were converted into the right to receive, in the aggregate, up to 5,248,536 unregistered shares of our common stock 1,049,706 of which were issued upon the closing of the acquisition. The remaining 4,198,830 shares will be issued after a hold back period of six months from the closing of the acquisition, less any shares deducted to satisfy indemnification obligations of the former Aires stockholders under the merger agreement. There are no milestone or earn-out payments under the merger agreement.

Inactive Development Programs

In prior years, we were focused on the development of ANX-514 (docetaxel for injectable emulsion) and Exelbine (vinorelbine injectable emulsion), which are novel emulsion formulations of currently marketed chemotherapy drugs. As a result of our current focus on MST-188, we elected to discontinue independent development of ANX-514 and Exelbine in 2012 and 2011, respectively, and are evaluating other opportunities for further development of these programs, such as partnering and licensing arrangements.

ANX-514 is a novel, detergent-free formulation of docetaxel, an intravenously-injected chemotherapy drug commonly used to treat solid tumors. Taxotere®, a branded formulation of docetaxel, is approved to treat breast, non-small cell lung, prostate, gastric, and head and neck cancers. ANX-514 was designed to have efficacy comparable to Taxotere without the non-active, toxic components found in Taxotere and without the corticosteroid premedication regimen required with Taxotere. In October 2011, we reached agreement with the FDA on a pivotal study for ANX-514 that would support approval of ANX-514 without a corticosteroid premedication regimen. We agreed on a 400-patient, non-inferiority study with a primary objective of comparing fluid retention following treatment with ANX-514, administered without corticosteroid premedication, and Taxotere, administered with corticosteroid premedication. However, in 2012, in accordance with our strategy to focus on MST-188, we determined not to initiate any clinical studies of ANX-514 in the foreseeable future.

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Exelbine is a novel emulsion formulation of the chemotherapy drug vinorelbine. Navelbine®, a branded formulation of vinorelbine, is approved in the U.S. to treat advanced non-small cell lung cancer as a single agent or in combination with cisplatin, and approved in the European Union to treat non-small cell lung cancer and advanced or metastatic breast cancer. In August 2011, we received a complete response letter from the FDA regarding the new drug application we submitted in November 2010 seeking approval of Exelbine for the same indications as Navelbine. The FDA stated that it could not approve the Exelbine NDA in its present form and that the bioequivalence study we had sponsored would need to be repeated because the authenticity of the drug products used in the bioequivalence trial could not be verified in accordance with FDA standards. Notably, at a meeting with the FDA following our receipt of the complete response letter, FDA staff commented that no clinical deficiencies were noted with the bioequivalence study and that there were no comments regarding our conclusion that Exelbine and Navelbine are bioequivalent. However, we elected to discontinue independent development of Exelbine and are seeking a partner or outside investor for the program to complete the necessary bioequivalence study.

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 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; and

FDA review and approval of the NDA prior to any commercial marketing or sale of the drug product in the U.S.

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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. The clinical

study sponsor may also suspend or terminate a clinical study based on evolving business objectives, competitive climate and/or lack of funds.

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.

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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 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.

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 may be 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.

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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.

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Pharmaceutical Pricing and Reimbursement

Significant uncertainty exists as to the 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 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 reimburse a product may be separate from the process of seeking approval of the product or for setting the price of the product. 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 our products or 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.

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 healthcare information and data privacy protection laws and fraud and abuse laws, such as anti-kickback and false claims statutes. 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 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 exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions 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 exemption or safe harbor. Under the new Physician Payment Sunshine Act requirements, we will be subject in the future to reporting payments made to certain investigators and physicians.

Federal false claims laws prohibit any person 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. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for 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 majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

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.

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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 $12.9 million in 2013 and $8.1 million in 2012. Our research and development expenses for 2013 and 2012 consisted primarily of costs associated with preparing for and conducting the EPIC and the TQT studies of MST-188, including research-related manufacturing and regulatory affairs and quality assurance-related consulting services. 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, 2014, Mast Therapeutics has 21 employees, all of which are full time, and Aires Pharmaceuticals, a wholly-owned subsidiary, has four employees, three of which are full-time. Our employees are not unionized and we believe that our relationship with our employees is good.

Our headcount has more than quadrupled since 2009, as we built out our management team and filled key positions in clinical operations, CMC, regulatory affairs, and finance and accounting. For at least the next few years, we plan to continue to operate by relying on a relatively small employee base and outsourcing key product development activities, including aspects of research-related manufacturing, clinical operations and regulatory affairs, as well as general and administrative activities, such as human resources, facilities, internal systems support and investor relations.

Formation

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

Trademarks

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

Available Information

Our website is located at *http://www.masttherapeutics.com*. Information found on our website is not incorporated by reference into this annual report on Form 10-K. We make our filings with the U.S. Securities and Exchange Commission, or SEC, including our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and any amendments 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*.

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Item 1A. Risk Factors.

Investment in our securities involves a high degree of risk. 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 development-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. We have accumulated net losses totaling approximately $208.7 million as of December 31, 2013, and 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 MST-188 and this product candidate may not receive regulatory approval or be successfully commercialized.

We currently have no products for sale and we are focusing our resources primarily on the development of MST-188. 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 this product candidate and our efforts, or those of a future partner, in this regard may prove unsuccessful. MST-188 requires considerable additional clinical development and significant manufacturing and related activities prior to commencing any commercial manufacturing, all of which require us to expend significant resources and with which we have limited experience. MST-188 may not be successful in the EPIC study or in other clinical studies we initiate, and, even if successful in clinical studies, may not receive regulatory approval in a timely manner, or at all. If MST-188 is approved by the FDA or any foreign regulatory agency, our ability to generate revenue from it will depend in substantial part on the extent to which it 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.

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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 $44.4 million as of December 31, 2013, 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 MST-188, AIR001 or other 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. Through our acquisition of Aires Pharmaceuticals in February 2014, we expanded our product pipeline to include AIR001. In the future, 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 in the next several years, and we will need to obtain additional capital to support our planned operating activities.

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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 MST-188 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. Between June 2009 and November 2011, we completed seven equity financings and, in February 2014, we commenced an at the market equity offering program 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.

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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 113,607,834 shares of our common stock outstanding as of March 24, 2014 and the closing price per share of our common stock on such date, which was $0.74, we could not raise more than approximately $16.7 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 our 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 our development of MST-188 or other 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 MST-188 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 MST-188 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.

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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 we are evaluating 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. We are highly dependent on certain personnel, including our chief executive officer, our president and chief operating officer, our chief medical officer, and our senior vice president, development. Our industries in general and our company in particular historically have experienced a high rate of turnover of management personnel. If we lose any of our key employees, our ability to successfully implement our current business strategy could be seriously harmed. Replacing key employees may be a difficult, costly and protracted process, particularly due to the fact that we currently do not have other executive officers or personnel to assume all of the responsibilities of these key employees. In addition, we may seek to increase the size of our organization as development 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 disrupt other development programs and distract 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.

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We may use cash, shares of our common stock, securities convertible into 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 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 MST-188 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.

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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 identified several ownership changes within the meaning of IRC Section 382 that had occurred during 2010 and 2011, with the most recent as a result of our November 2011 common stock and warrant financing. As a result of those ownership changes, 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. In addition, although we have not yet conducted a formal study to identify ownership changes within the meaning of IRC Section 382 for periods after December 31, 2011, we believe that the common stock and warrant financing we completed in June 2013 may be an ownership change for purposes of Sections 382 and 383 of the IRC, which would further limit the availability of our NOL carry forwards.

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 June 19, 2013. 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, we have limited capability to establish and maintain a comprehensive disaster recovery program and, accordingly, we do not have 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.

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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 MST-188 or 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.

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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 MST-188 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.

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, non-purified poloxamer 188 was tested in more than 2,000 human subjects in various indications before the program was discontinued, principally due to concerns regarding acute renal dysfunction observed in patients who received the study drug. In contrast, MST-188 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 compelling data from nonclinical and clinical studies of poloxamer 188 in multiple indications, ongoing and future studies may fail to demonstrate clinical benefits to human subjects.

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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. 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 MST-188 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. For instance, despite positive nonclinical testing that indicated bioequivalence between ANX-514 and the reference product, Taxotere, our bioequivalence study of ANX-514 did not demonstrate bioequivalence between ANX-514 and Taxotere based on the FDA s benchmark regulatory standards and the FDA determined ANX-514 could not be approved based on the findings from that study.

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, such data could adversely affect our or another licensee s development of our product candidates.

There is significant risk that our product candidates, including MST-188, could fail to show anticipated results in ongoing and future nonclinical testing and/or clinical studies 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 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 MST-188, 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 MST-188, 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.

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

Currently, we do not have alternative sources to backup our primary sources of clinical trial material. 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 MST-188 API, 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 MST-188 API on commercially reasonable terms, or at all. Production of the API in MST-188 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 MST-188 API starting material manufactures it under excipient-grade cGMP conditions. Prior to approval of MST-188, the FDA or other regulatory agencies may require our API starting material to be manufactured consistent with cGMP requirements applicable to API, in which case regulatory approval and commercialization of MST-188 could be delayed significantly and require substantial additional financial resources as we seek to contract with a third party to manufacture poloxamer 188 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 MST-188, which likely would add significant cost to the overall development and commercialization of MST-188 and adversely affect our ability to develop MST-188 on a timely basis.

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 API for future MST-188 clinical trial material or commercial product, the FDA may require us to conduct additional clinical and nonclinical studies to ensure comparability of the drug product containing API manufactured by our current CMO to API manufactured by the new supplier. In addition to the potential for such

requirements to result in significant interruption to development and commercialization of MST-188, 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, including MST-188, 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. 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.

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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 clinical studies, including EPIC or any other then-ongoing studies. 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, our current CMOs are located 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.

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. If these CROs and/or investigators fail to devote sufficient time and resources to our studies, 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 our 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, these CROs 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.

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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 non-purified poloxamer 188, 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 MST-188, 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 MST-188 in prior clinical studies. If in our clinical studies of MST-188 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 MST-188 or to investigate the clinical significance of the adverse event and MST-188 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, we have estimated that patient enrollment in EPIC will complete by the end of 2015. However, predicting the rate of enrollment 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.

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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 in addition to EPIC prior to its review or approval of MST-188 in sickle cell disease. If the development plan for MST-188 or any other 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 current good manufacturing practices, or cGMP, and other regulatory standards. 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;

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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.

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 MST-188 or any other product candidate obtains regulatory approval.

We currently have limited marketing capabilities and no sales capability and our company has never marketed or sold products. To commercialize MST-188 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;

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- 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 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;

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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.

For exclusivity for our product candidates in rare or orphan diseases, such as MST-188 in sickle cell disease and acute limb ischemia, we expect to rely primarily on orphan drug designation in the U.S. and European Union. However, orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review or approval process. Our product candidates may not receive the marketing exclusivity periods available with orphan drug status if they are not the first drug products to obtain marketing approval for the treatment of the disease or condition for which they received the orphan designation. In addition, orphan drug exclusive marketing rights may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantity of the drug. Furthermore, if the FDA later determines another drug or biologic to be clinically superior to or different from our product for treatment of disease or condition for which it received orphan status, the FDA may approve such other product for marketing during our product s exclusivity period.

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 for our product candidates, including MST-188, may be difficult to obtain and any issued claims may be limited.

We have filed for patent protection covering our proprietary supercritical fluid extraction process, methods of using poloxamers in various clinical settings, and the use of poloxamers in combination therapy. However, these patent applications cover only methods of manufacturing, methods of using MST-188, and combination therapeutic methods; they do not cover the underlying API. Claims covering the API are widely viewed as the strongest form of intellectual property protection for pharmaceutical products, as they apply without regard to how the API is manufactured, used or formulated.

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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 poloxamer 188 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 MST-188 in that indication may be unpatentable.

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, one or more parties may independently develop similar technologies or duplicate our technologies or design around the patented aspects of our technologies. 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

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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 MST-188 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 privately-held companies, GlycoMimetics, Inc. and Selexys Pharmaceuticals Corporation, respectively, which have clinical-stage agents for the treatment of vaso-occlusive crisis. Pfizer is expected to commence a phase 3 study of GlycoMimetics GMI-1070 in vaso-occlusive crisis of sickle cell disease in the second half of 2014. 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. Further, in March 2014, Emmaus Life Sciences, Inc. disclosed that top-line data from its phase 3 clinical study of L-glutamine in sickle cell disease showed a statistically significant reduction in the frequency of sickle cell crisis and announced its plans to submit an NDA in mid-2014 for marketing approval of L-glutamine to treat patients with sickle cell disease. Additionally, 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. If an effective treatment or cure for vaso-occlusive crisis or sickle cell disease receives regulatory approval, the potential commercial success of MST-188 could be severely jeopardized.

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With respect to competition for MST-188 for complications of arterial disease, although we intend first to develop MST-188 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, certain of which are in late-stage clinical development. Should any of these other investigational therapies receive regulatory approval prior to MST-188, they may become entrenched in the standard of care, diminish the need for MST-188, 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 reimbursement for the costs of such products and related treatments will be available from government health administration authorities, private health insurers and other third-party payors. Significant uncertainty exists as to the reimbursement status of newly approved medical products. 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. These payors are increasingly attempting to contain healthcare costs by limiting both coverage and the level of reimbursement, particularly for new therapeutic products or if there is a perception that the target indication of the new product is well-served by existing drugs or other treatments. Accordingly, even if coverage and reimbursement are provided, market acceptance of our products would be adversely affected if the level of coverage and/or reimbursement for our products proved to be unprofitable for healthcare providers or less profitable than alternative treatments.

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. While we cannot predict the outcome of current or future legislation, we anticipate that the U.S. Congress and state legislatures will continue to introduce initiatives 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 if future legislative proposals, whether domestic or abroad, will be adopted that might affect our products or 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. Any such healthcare reforms could have a material and adverse effect on the marketability of any products for which we ultimately receive FDA or other regulatory agency approval.

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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 would 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.

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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, and has traded at under $1.00 per share for more than twelve consecutive months. 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. The delisting of our common stock may also materially impair our stockholders ability to buy and sell shares of our common stock. In addition, the delisting of our common stock could significantly impair our ability to raise capital, which is critical to the execution of 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;
- FDA or international regulatory actions and regulatory developments in the U.S. and foreign countries;

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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;

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 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 clinical studies of MST-188 and regulatory agency decisions affecting development of MST-188.

We expect announcements of progress with and results of clinical studies of MST-188 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 of MST-188 or MST-188 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.

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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 drop 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 an at the market offering program, or ATM program, under which we may sell shares of our common stock having an aggregate offering price of up to $30 million, and 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 $120 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 44 million additional shares of our common stock and warrants to purchase more than 28 million of those shares have an exercise price of $0.65 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 drop 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 such 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 2.1% of our outstanding common stock (based on shares outstanding as of March 24, 2014), 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 MST-188 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 upon completion of the Aires acquisition in February 2014 and to vote any additional shares that may be issued (up to 4,198,830 shares in the aggregate) at the end of the six-month holdback period 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, as well as issuance of the full amount of the holdback shares under our merger agreement with Aires, based on 113,607,834 shares of our common stock outstanding as of March 24, 2014, we would have voting control with respect to approximately 14.2% 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.

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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, 2013, more than 329 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 expand our product pipeline. We are also authorized to issue up to 1,000,000 shares of preferred stock, without stockholder approval. The preferred stock may have rights that are superior to the rights of the holders of our common stock, at a purchase price then approved by our board of directors. The sale or the proposed sale of substantial amounts of our common stock or

preferred stock in the public markets may adversely affect the market price of our common stock and our stock price. Our stockholders may also experience substantial dilution

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Item 1B. Unresolved Staff Comments.

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

Item 2. Properties.

We lease approximately 9,300 square feet of office space for our headquarters in San Diego, California. That lease will expire in January 2015, unless we exercise our option to extend through October 2018. We believe that the facilities we lease are adequate to meet our current requirements and our requirements for the remaining term of the lease. We have no laboratory, research or manufacturing facilities.

Item 3. Legal Proceedings.

In the normal course of business, we may become subject to lawsuits and other claims and proceedings. Such matters are subject to uncertainty and outcomes are often not predictable with assurance. We are not currently a party to any material pending litigation or other material legal proceeding.

Item 4. Mine Safety Disclosures.

Not applicable.

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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 periods presented in the following table, 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			
	2013		2012	
	High	Low	High	Low
First Quarter	$ 0.82	$ 0.56	$ 0.75	$ 0.56
Second Quarter	$ 0.76	$ 0.41	$ 0.70	$ 0.45
Third Quarter	$ 0.52	$ 0.40	$ 0.87	$ 0.49
Fourth Quarter	$ 0.55	$ 0.40	$ 0.80	$ 0.54

As of March 24, 2014, we had approximately 151 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 and, on February 28, 2014, pursuant to the terms of the merger agreement, we issued an aggregate of

1,049,706 shares of our common stock to former stockholders of Aires.

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.

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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 28, 2013, the last business day of our most recently completed second fiscal quarter, 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 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, our lead product candidate, for serious or life-threatening diseases and conditions typically characterized by impaired microvascular blood flow and damaged cell membranes. We recently acquired Aires Pharmaceuticals, which is developing AIR001 (sodium nitrite) inhalation solution, and we are in the process of determining the optimal development strategy for this new asset.

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 losses since inception. We incurred losses from operations of $21.5 million and $15.6 million for the years ended December 31, 2013 and December 31, 2012, respectively. Our cash, cash equivalents and investment securities were $44.4 million as of December 31, 2013.

We continue to focus our resources primarily on MST-188. We believe that its pharmacologic effects support its development in a wide range of diseases and conditions and we intend to develop MST-188 in multiple clinical indications, both independently and through collaborations. In May 2013, we began enrolling subjects in EPIC, a pivotal phase 3 study of MST-188 in patients with sickle cell disease, and enrollment of that study is one of our top priorities. In March 2014, we initiated a phase 2, clinical proof-of-concept study of MST-188 in combination with recombinant tissue plasminogen activator (rt-PA) in patients with acute lower limb ischemia to evaluate whether MST-188 improves effectiveness of rt-PA therapy. In addition, our MST-188 pipeline includes development programs in heart failure and resuscitation following major trauma (i.e., restoration of circulating blood volume and pressure).

We anticipate that our cash, cash equivalents and investment securities will be sufficient to fund our operations for at least the next 12 months. However, we have based this estimate on significant assumptions and we could utilize our available financial resources sooner than we currently expect. For example, we may 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 financial resources will sustain us. We expect to incur significant and increasing losses for the next several years as we advance our product candidates through clinical studies and other development activities and seek regulatory approval for commercialization. We will need additional capital to support our planned operating activities.

In addition, we may seek to expand our product pipeline through acquisition of additional product candidates and/or technologies. We expect that our capital requirements will increase in future periods if we determine to pursue clinical development of AIR001 without a partner, or if we determine to conduct studies of MST-188 in addition to those currently planned or pursue development of MST-188 in additional indications, or if we determine to 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 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.

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Acquisition of Aires Pharmaceuticals

Merger Consideration. On February 27, 2014, we completed the acquisition of Aires Pharmaceuticals, Inc., a privately-held Delaware 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. Aires lead product candidate, AIR001 (sodium nitrite) inhalation solution, is an intermittently nebulized formulation of nitrite with orphan drug designation in the U.S. and European Union for the treatment of pulmonary arterial hypertension. Upon completion of the merger, we issued an aggregate of 1,049,706 unregistered shares of our common stock to former Aires stockholders and, following a six-month holdback period, we will issue up to 4,198,830 additional unregistered shares of our common stock, in the aggregate, to former Aires stockholders, subject to adjustment to satisfy indemnification obligations of the former Aires stockholders to us, if any, in accordance with the merger agreement. There are no milestone or earn-out payments under the merger agreement; therefore, the total merger consideration will not exceed 5,248,536 shares, or 5% of the shares of our common stock outstanding as of the closing date.

Stockholder Agreement. On February 7, 2014, we also entered into a stockholder agreement with the holders of all outstanding shares of Aires preferred stock and approximately 90% of the outstanding shares of Aires common stock. The transfer restrictions aspect of this agreement, among other things, prohibits the stockholder parties from transferring any shares acquired from us pursuant to the merger agreement for a period of six months from the closing date of the merger, subject to certain exceptions.

In-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, or 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) $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.

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 MST-188. 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 designated the repurchased shares as treasury stock. 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 MST-188 achieves certain milestones, with 3,839,400 shares issuable upon the FDA s acceptance for review of a NDA covering the use of purified poloxamer 188 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.

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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 consolidated 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 acquired in-process research and development, or IPR&D, goodwill and recognition of expenses for clinical study accruals 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 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 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.

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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 price consists entirely of shares of our common stock, we calculate the purchase price by determining the probability-weighted fair value as of the acquisition date of shares issued and issuable, if applicable, pursuant to the terms of the agreement governing the business combination. If the transaction involves contingent consideration based on achievement of milestones or earn-out events, 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.

Accounting for business combinations requires us to make significant estimates and assumptions, particularly with respect to the fair value of any contingent consideration or acquired IPR&D. These calculations typically are highly judgmental and it is possible that other professionals, applying reasonable judgment to the same facts and circumstances, would develop and support a range of alternative estimated amounts. For instance, in accounting for our acquisition of SynthRx, we used a discounted cash flow model to determine the fair value of the contingent consideration, though other methodologies could have been used. Discounted cash flow models require the use of significant estimates and assumptions, including, but not limited to: the probability of clinical and regulatory success for a product candidate considering its stage of development; the time and resources needed to complete the development and approval of a product candidate, including the inherent difficulties and uncertainties in developing a product candidate, such as obtaining FDA and other regulatory approvals; estimated cash flows projected following the approval of a product candidate in development; the commercial life of the potential approved product and associated risks; and risks associated with uncertainty regarding achievement of the milestone or earn-out events. Changes in any of such estimates and assumptions could significantly impact the fair values recorded for assets acquired and liabilities assumed, resulting in significant charges to our operations. In addition, unanticipated events and circumstances may occur which may affect the accuracy or validity of such assumptions, estimates or actual results.

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 on September 30 of each year. 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.

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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 MST-188 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.

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 began maintaining such expenses by type on January 1, 2005. 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, including process development activities, and quality assurance and regulatory affairs services. Research-related manufacturing expenses include costs associated with 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.

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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 an 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, a new drug application, or 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 as we continue EPIC, our phase 3 clinical study of MST-188 in sickle cell disease, and initiate and conduct additional studies of MST-188, including the phase 2 clinical study in acute limb ischemia that we initiated in March 2014, as well as perform additional manufacturing process development activities and manufacture additional clinical trial material. As a result, we expect our R&D expenses to increase significantly in 2014 relative to 2013.

Selling, General and Administrative Expenses. Selling, general and administrative, or SG&A, expenses consist primarily 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.

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We expect SG&A expenses in 2014 to remain consistent relative to 2013.

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 also include the changes in the fair value of the contingent asset and 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 2013 and 2012

Revenue. We recognized no revenue for the years ended December 31, 2013 and December 31, 2012.

Operating Expenses. The following table illustrates the types of operating expenses we incurred in 2013 and 2012 and their respective percent of our total operating costs for those periods:

	Operating Expenses Years Ended December 31,	
	2013	2012
Research and development	60%	52%
Selling, general and administrative	40%	48%
Transaction-related expenses	0%	0%
Depreciation and amortization	0%	0%
Total operating expenses	100%	100%

R&D Expenses. In 2013, our most significant R&D expenses were external costs associated with the EPIC study and our QT/QTc study of MST-188. These expenses consisted primarily of costs associated with CRO expenses, clinical study-related consulting and U.S. investigative site expenses, which include start-up costs as well as patient expenses. In 2012, our most significant R&D expenses were third-party fees and expenses that related primarily to generating MST-188 clinical trial material and preparing for the EPIC study.

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 2013 and 2012:

	Years Ended December 31,				January 1, 2005 through December 31,
	2013	%	2012	%	2013

External clinical study fees and expenses	$ 7,524,311	58%	$ 1,328,201	16%	$ 33,621,810
External nonclinical study fees and expenses	2,797,472	22%	4,688,770	58%	38,953,509
Personnel costs	2,409,095	19%	1,993,405	25%	15,763,541
Share-based compensation expense	171,385	1%	77,776	1%	3,146,606
Total	$ 12,902,263	100%	$ 8,088,152	100%	$ 91,485,466

R&D expenses increased by $4.8 million, or 59.5%, to $12.9 million for the year ended December 31, 2013, compared to $8.1 million for the year ended December 31, 2012. The increase in R&D expenses in 2013 compared to 2012 was due to a $6.2 million increase in external clinical study fees and expenses, a $0.4 million increase in personnel costs and a $0.1 million increase in share-based compensation expense, offset by a $1.9 million decrease in external nonclinical study fees and expenses. The $6.2 million increase in external clinical study fees and expenses was related primarily to 1) a $4.1 million increase in EPIC study costs, primarily for CRO expenses and U.S. investigative site expenses, 2) a $1.8 million increase related to QT/QTc study expenses, and 3) a $0.3 million increase related to preparing to initiate our phase 2 study in ALI. The $0.4 million increase in personnel costs resulted primarily from additional clinical and research-related manufacturing staff hired in late 2012 and 2013. The $1.9 million decrease in external nonclinical study fees and expenses resulted primarily from a $1.7 million decrease in research-related manufacturing activities for ANX-514, which we discontinued in 2012, and a $0.2 million decrease in research-related manufacturing activities for MST-188.

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Selling, General and Administrative Expenses. In 2013 and 2012, our SG&A expenses consisted primarily 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 13.3%, to $8.5 million for the year ended December 31, 2013, compared to $7.5 million for the year ended December 31, 2012. This increase resulted from a $0.7 million increase in consulting and legal services fees and a $0.3 million increase in personnel costs, mainly due to additional staff hired in 2013. The increase in consulting and legal services fees was due primarily to increases in investor relations, market strategy and research, and business development activities and patent and other legal counsel expenses.

Transaction-Related Expenses. Transaction-related expenses were $0.1 million for the year ended December 31, 2013, compared to negative, ($0.1) million for the year ended December 31, 2012. 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).

We recognized transaction-related expenses for the year ended December 31, 2012 due to changes in the fair values of our contingent asset and contingent liability at December 13, 2012 and December 31, 2012, respectively, compared to December 31, 2011. The contingent asset and contingent liability both related to contingent consideration for the SynthRx acquisition. The contingent asset was settled on December 13, 2012 by our repurchase of 1,454,079 shares of our common stock from the former SynthRx stockholders, and we remeasured its fair value as of that date. The contingent liability was not settled during 2012 and, consequently, we remeasured its fair value as of December 31, 2012. The changes in the fair values of the contingent asset and contingent liability were due to updated estimates at the time regarding the probability and circumstances of achievement of the first milestone under the merger agreement and the differences in our stock price at December 13, 2012 ($0.61 per share) and December 31, 2012 ($0.57 per share) relative to December 30, 2011 ($0.59 per share), which was the last trading day of 2011.

Net Loss. Net loss was $21.5 million, or $0.28 per share (basic and diluted), for the year ended December 31, 2013, compared to a net loss of $15.6 million, or $0.33 per share (basic and diluted), for the year ended December 31, 2012.

Liquidity and Capital Resources

We have a history of generating 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, 2013 and 2012, we incurred losses from operations of $21.5 million and $15.6 million, respectively. Our cash, cash equivalents and investment securities were $44.4 million at December 31, 2013.

We historically have funded our operations principally through proceeds from sales of our equity securities. We did not conduct any capital-raising transaction in 2012. 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.

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We may receive up to $0.8 million, $6.6 million, $5.6 million, $11.7 million and $18.3 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 and June 2013, 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 and $0.65 per share, respectively. In comparison, the closing sale price of our common stock on March 24, 2014 was $0.74 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. As of March 24, 2014, we had sold and issued an aggregate of 9,847,842 shares at a weighted-average sales price of $0.83 per share under the ATM program for aggregate gross proceeds of $8.2 million. After deducting sales agent commission and discounts, such proceeds totaled $8.0 million.

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

Analysis of our 2013 versus 2012 cash flow from operating, investing and financing activities is provided below.

	December 31, 2013	Increase During 2013	December 31, 2012
Cash, cash equivalents and investment securities	$ 44,392,540	$ 7,881,138	$ 36,511,402
Net working capital	$ 40,694,652	$ 6,091,656	$ 34,602,996

	Year Ended December 31, 2013	Change Between Periods	Year Ended December 31, 2012
Net cash used in operating activities	$ (17,788,962)	$ (3,870,094)	$ (13,918,868)
Net cash used in investing activities	$ (4,765,816)	$ 2,399,359	$ (7,165,175)
Net cash provided by financing activities	$ 25,736,952	$ 25,736,212	$ 740

***Operating activities*.** Net cash used in operating activities was $17.8 million in 2013, compared to $13.9 million in 2012. The increase in cash used in operating activities in 2013 was due primarily to a higher net loss in 2013 as compared to 2012 ($5.9 million), which was attributable primarily to increases in our R&D expenses in connection with MST-188 development activities, an increase in prepaid and other assets ($0.1 million) and a decrease in depreciation and amortization expense ($0.1 million), offset by an increase in our accounts payable and accrued liabilities ($2.4 million), an increase in the loss on the change in fair value of contingent consideration related to our SynthRx acquisition ($0.1 million) and an increase in share-based compensation expense ($0.1 million). The increase in accounts payable and accrued liabilities was primarily related to increased accruals for services provided by our CROs and CMOs and higher compensation-related accruals due to the timing of payments. We also incurred a $0.4 million equipment impairment charge in 2012 related to ANX-514 manufacturing equipment.

Investing activities. Net cash used in investing activities was $4.8 million in 2013, compared to $7.2 million in 2012. The difference was due primarily to an increase of $6.1 million in purchases of certificates of deposit, offset by $8.3 million in maturities and sales of certificates of deposits and a $0.2 million decrease in purchases of property and equipment.

Financing activities. Net cash provided by financing activities was $25.7 million in 2013, compared to $740 in 2012. The cash provided by financing activities in 2013 consisted of proceeds from the underwritten public offering of our equity securities completed in June 2013.

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Management Outlook

We anticipate that our cash, cash equivalents and investment securities will be sufficient to fund our currently planned level of operations for at least the next 12 months. However, our estimate of the period of time through which our current financial resources will be adequate to support our operations is a forward-looking statement based on significant assumptions that involve a number of risks and uncertainties and actual results could differ materially. Factors that will affect our future capital requirements include, but are not limited to: the progress and results of our clinical and nonclinical studies of MST-188, particularly the EPIC study and the phase 2 study in acute limb ischemia; the number and nature of indications and jurisdictions in which we pursue development and regulatory approval of MST-188, and the extent to which we do so independently or through collaborations; our development strategy for AIR001; the rate of progress and costs of development and regulatory approval activities associated with our product candidates, including expenses related to initiating and conducting clinical studies and research-related manufacturing expenses; the extent to which we increase our workforce; the extent to which we seek to commercialize and sell our product candidates, if approved, independently or through collaborations; the extent of commercial success of any of our product candidates for which we receive regulatory approval; the costs and timing of establishing commercial manufacturing supply arrangements for our product candidates and establishing or acquiring sales and distribution capabilities for any approved products; and the extent to which we seek to expand our product pipeline through acquisitions and execute on transactions intended to do so.

MST-188

We are focusing our resources primarily on development of MST-188. 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 40 in the U.S. and 30 outside the U.S. At the end of 2013, we had opened 40 U.S. sites and, since then, we have opened clinical sites in multiple jurisdictions outside of the U.S. We expect to have approximately 25 sites open outside of the U.S. by the end of 2014. Although predicting the rate of enrollment for EPIC is subject to a number of significant assumptions and the actual rate may differ materially, we expect to complete enrollment by the end of 2015. We estimate that external clinical study fees and expenses from January 2014 through completion of the EPIC study will be approximately $16 million.

In addition to enrolling subjects in EPIC, we are conducting activities to evaluate the potential of MST-188 to reduce organ damage and improve survival in patients with sickle cell disease. First, we plan to conduct a sub-study at select EPIC sites to investigate and quantify the effect of MST-188 on microvascular blood flow, indirectly measured by tissue oxygenation using a non-invasive method, and we will evaluate the relationship between tissue oxygenation and clinical outcomes, such as the duration of vaso-occlusive crisis. Approximately 30 patients who are concurrently randomized in EPIC will be enrolled in the sub-study. We submitted the protocol for the sub-study to the FDA in 2013 and plan to initiate it during the second quarter of 2014. The estimated external clinical study fees and expenses to conduct the sub-study are included in the estimated cost of EPIC stated above.

We are conducting the pilot phase of a nonclinical study in a transgenic mouse model of sickle cell disease. The objective of this study is to demonstrate that chronic intermittent administration of MST-188 reduces the accumulating burden of organ damage and prolongs survival. The transgenic mice express human sickle hemoglobin and have been shown to mirror the pathophysiology and disease progression of sickle cell disease typically seen in humans, including development of neuropathy, organ damage and premature death. The results of this study, coupled with the clinical pharmacodynamic data from the EPIC sub-study described above, may provide the best evidence of MST-188 s ability to improve long-term outcomes, where direct evaluation of those outcomes is impractical. We expect to complete this study, including the survival portion, in late 2015.

In March 2014, we initiated a phase 2, clinical proof-of-concept study of MST-188 in combination with rt-PA in acute limb ischemia, or ALI. The study will enroll approximately 60 patients with acute lower limb ischemia from approximately 15 sites within and outside the U.S. and compare a high dose and low dose of MST-188 in combination with rt-PA against rt-PA alone. We estimate that the study will take approximately 18 months to enroll and that external clinical study fees and expenses for the study will be approximately $4 million. If this phase 2 study in ALI demonstrates that MST-188 improves the clot busting activity of rt-PA, we believe it not only would progress development in that indication, but also generate interest in developing MST-188 in other manifestations of occlusive arterial disease, such as stroke. Therefore, in parallel to the phase 2 study in ALI, we plan to conduct a nonclinical study in an experimental model of thrombotic stroke to evaluate MST-188 s potential to expand the window in which rt-PA is effective and improve the therapeutic effect of rt-PA.

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We also are evaluating MST-188 s potential in heart failure, another area of significant unmet medical need. Although there have been modest improvements in treatment, acute decompensated heart failure remains associated with high mortality and high hospital admission and readmission rates in patients older than 65 years. In contrast with current treatments, such as vasodilators and beta blockers, which can indirectly improve heart function, MST-188 s membrane sealant and hemorheologic activity may directly improve heart contractility and function. Earlier this year, we announced positive results from a randomized, placebo-controlled, nonclinical study of MST-188 in a model of chronic heart failure. Encouraged by those results, we are evaluating options for clinical development of MST-188 in heart failure. We plan to submit an investigational new drug application to the FDA covering the use of MST-188 in heart failure in the summer of 2014 and, if FDA feedback is positive, we expect to initiate a phase 2, dose-finding, clinical study of MST-188 in patients with heart failure in the first half of 2015. Our preliminary estimate of external clinical study fees and expenses for the phase 2 study is approximately $3 million; however, we are still early in the planning process and this estimate may change. We do not expect 2014 external clinical study fees and expenses related to the MST-188 heart failure program to be material.

In addition, we are evaluating MST-188 s potential in resuscitation following major trauma (i.e., restoration of circulating blood volume and pressure). Based on feedback from U.S. Department of Defense personnel, during 2014, we plan to conduct a nonclinical study of MST-188 in an experimental model of trauma. The results of this study, if positive, may generate further interest from the Department of Defense in evaluating the utility of MST-188 as a resuscitation fluid following major trauma.

Finally, we are conducting or plan to conduct a number of other *ex vivo*, nonclinical *in vivo* and *in vitro* studies of MST-188 to further understand its pharmacologic effects and support our intellectual property positions.

AIR001

In February 2014, we acquired Aires Pharmaceuticals, Inc., which is developing AIR001, an intermittently nebulized form of sodium nitrite to treat pulmonary vascular disorders, such as pulmonary hypertension (PH). Over the next several months, we will continue to confer with clinical and regulatory experts in PH and heart disease to define the optimal development strategy for AIR001. In parallel, we will review data from the approximately 20 subjects who completed treatment in a phase 2 study of AIR001 in pulmonary arterial hypertension, which, as a result of capital constraints, Aires had been in the process of closing prior to the acquisition, and we plan to support expansion of an ongoing, university-sponsored phase 2a study of AIR001 in WHO Group 1 and WHO Group 3 PH to patients with PH associated with heart failure (WHO Group 2 PH). We estimate that, during the 12-month period following the acquisition of Aires, costs of the AIR001 program, including costs to wind-down the phase 2 studies in PAH, support the expansion of the university-sponsored phase 2a study, Aires personnel costs and consulting fees, will be approximately $2 million. However, as we refine our development strategy for AIR001 over the next few months, we expect that our initial plans for the program, and, therefore, its estimated costs, will change. In particular, we are aware of other planned investigator-sponsored clinical studies of AIR001 in WHO Group 2 PH patients and we may determine to provide some level of support to those studies, which could increase our current estimate of program costs.

In parallel with our independent development of MST-188 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 successful development and commercialization of MST-188 or AIR001. In addition, our

capital requirements likely will increase in future periods as we progress development of MST-188 in currently planned indications and potentially pursue its development in additional indications and define our development strategy for AIR001. Further, our capital requirements would likely increase if we were to 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. Even though we were able to raise significant funds in the recent past through equity financings, adequate additional financing 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.

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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, 2013. Based on that evaluation, our principal executive officer and principal financial officer have concluded that as of December 31, 2013 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, 2013 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 based on the framework in *Internal Control Integrated Framework (1992)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under the framework in *Internal Control Integrated Framework*, our management concluded that our internal control over financial reporting was effective as of December 31, 2013.

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.

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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 2014 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.

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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, 2013 and 2012

Consolidated Statements of Operations and Comprehensive Income/(Loss) for the years ended December 31, 2013 and 2012 and from inception (June 12, 1996) through December 31, 2013

Consolidated Statements of Stockholders Equity (Deficit) from inception (June 12, 1996) through December 31, 2013

Consolidated Statements of Cash Flows for the years ended December 31, 2013 and 2012 and from inception (June 12, 1996) through December 31, 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.

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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 26, 2014

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, Patrick L. Keran 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 26, 2014
/s/ Brandi L. Roberts Brandi L. Roberts	Chief Financial Officer and Senior Vice President (Principal Financial and Accounting Officer)	March 26, 2014
/s/ Jack Lief Jack Lief	Chair of the Board	March 26, 2014
/s/ David A. Ramsay David A. Ramsay	Director	March 26, 2014
/s/ Lewis J. Shuster Lewis J. Shuster	Director	March 26, 2014

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Index to Consolidated Financial Statements

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

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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 as of December 31, 2013 and 2012, the related consolidated statements of operations and comprehensive income/(loss), and of cash flows for the years then ended, and the related consolidated statements of stockholders equity (deficit) for each of the three years in the period ended December 31, 2013 present fairly, in all material respects, the financial position of Mast Therapeutics, Inc. and its subsidiaries (a development stage enterprise) at December 31, 2013 and 2012, the results of their operations and their cash flows for the years then ended, and financial position and operations cumulatively from January 1, 2011 through December 31, 2013 (not separately presented) 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 26, 2014

See accompanying notes to consolidated financial statements.

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Mast Therapeutics, Inc. and Subsidiaries

(A Development Stage Enterprise)

Consolidated Balance Sheets

	December 31, 2013	December 31, 2012
Assets		
Current assets:		
Cash and cash equivalents	$ 25,681,092	$ 22,500,440
Investment securities	18,711,448	14,010,962
Prepaid expenses and other current assets	1,135,490	662,260
Total current assets	45,528,030	37,173,662
Property and equipment, net	105,747	198,358
In-process research and development	6,549,000	6,549,000
Goodwill	3,006,883	3,006,883
Other assets	60,312	43,912
Total assets	$ 55,249,972	$ 46,971,815
Liabilities and Stockholders Equity		
Current liabilities:		
Accounts payable	$ 963,947	$ 698,838
Accrued liabilities	2,495,088	1,283,976
Accrued compensation and payroll taxes	1,374,343	445,352
Contingent liability		142,500
Total current liabilities	4,833,378	2,570,666
Deferred income tax liability	2,608,755	2,608,755
Total liabilities	7,442,133	5,179,421
Commitments (Note 10)		
Stockholders equity:		
Common stock, $0.001 par value; 500,000,000 shares authorized; 102,710,286 and 47,719,365 shares issued at December 31, 2013 and 2012, respectively; 102,710,286 and 46,265,286 shares outstanding at December 31, 2013 and 2012, respectively	102,710	47,720
Treasury stock, at cost 1,454,079 shares at December 31, 2012		(1,454)
Additional paid-in capital	254,154,693	226,696,863
Accumulated other comprehensive loss	(20,738)	(2,194)
Deficit accumulated during the development stage	(206,428,826)	(184,948,541)
Total stockholders equity	47,807,839	41,792,394

Total liabilities and stockholders equity	$ 55,249,972	$ 46,971,815

See accompanying notes to consolidated financial statements.

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Mast Therapeutics, Inc. and Subsidiaries

(A Development Stage Enterprise)

Consolidated Statements of Operations and Comprehensive Income/(Loss)

	Years Ended December 31,		Inception (June 12, 1996) Through December 31,
	2013	2012	2013 (Unaudited)
Revenues:			
Net sales	$	$	$ 174,830
Licensing revenue			1,300,000
Grant revenue			618,692
Total net revenue			2,093,522
Cost of goods sold			51,094
Gross margin			2,042,428
Operating expenses:			
Research and development	12,902,263	8,088,152	98,959,719
Selling, general and administrative	8,517,781	7,519,405	76,184,493
Transaction-related expenses	79,640	(69,602)	751,292
Depreciation and amortization	39,517	90,047	11,064,752
Write-off of in-process research and development			10,422,130
Goodwill impairment			5,702,130
Equity in loss of investee			178,936
Total operating expenses	21,539,201	15,628,002	203,263,452
Loss from operations	(21,539,201)	(15,628,002)	(201,221,024)
Reduction of fair value of warrants			(12,239,688)
Interest income	60,268	73,560	4,892,476
Interest expense			(191,729)
Other income (expense), net	(1,352)	(5,047)	128,353
Loss before cumulative effect of change in accounting principle	(21,480,285)	(15,559,489)	(208,631,612)
Cumulative effect of change in accounting principle			(25,821)

Net loss	(21,480,285)	(15,559,489)	(208,657,433)
Preferred stock dividends			(621,240)
Deemed dividends on preferred stock			(10,506,683)
Net loss applicable to common stock	$ (21,480,285)	$ (15,559,489)	$ (219,785,356)
Loss per common share basic and diluted	$ (0.28)	$ (0.33)	
Weighted average shares outstanding basic and diluted	76,585,752	47,641,043	
Comprehensive Income/(Loss):			
Net loss	$ (21,480,285)	$ (15,559,489)	$ (208,657,433)
Unrealized gains (losses) on marketable securities	(18,544)	104	(18,582)
Foreign currency translation adjustments			(2,156)
Comprehensive net loss	$ (21,498,829)	$ (15,559,385)	$ (208,678,171)

See accompanying notes to consolidated financial statements.

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Mast Therapeutics, Inc. and Subsidiaries

(A Development Stage Enterprise)

Consolidated Statements of Stockholders Equity (Deficit)

Inception (June 12, 1996) Through December 31, 2013

	Cumulative convertible preferred stock, series A through C		Cumulative convertible preferred stock, series A (2009)		Cumulative convertible preferred stock, series B through F (2009 - 2010)		Common stock				Deficit		
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated during development stage	Treasury stock, at cost	Total stockholders equity (deficit)
Balances at June 12, 1996 (date of incorporation)	$	$		$		$		$	$	$	$	$	$
Sale of common stock without par value							20		10				10
Issuance of common stock and net liabilities assumed in acquisition							68,645	69	4,871		(18,094)		(13,154)
Issuance of common stock							80,405	80	2,386		(2,466)		
Net loss											(259,476)		(259,476)
Balances at December 31, 1996 (unaudited)							149,070	149	7,267		(280,036)		(272,620)
Sale of common stock, net of offering costs of $9,976							40,182	40	1,790,939				1,790,979

Issuance of common stock in acquisition			15,036	15	888,235	888,250
Minority interest deficiency at acquisition charged to the Company					(45,003)	(45,003)
Net loss					(1,979,400)	(1,979,400)
Balances at December 31, 1997 (unaudited)			204,288	204	2,686,441	(2,304,439)	382,206
Rescission of acquisition			(15,036)	(15)	(888,235)	561,166	(327,084)
Issuance of common stock at conversion of notes payable			18,011	18	363,982		364,000
Expense related to stock warrants issued					260,000		260,000
Net loss						(1,204,380)	(1,204,380)
Balances at December 31, 1998 (unaudited)			207,263	207	2,422,188	(2,947,653)	(525,258)
Sale of common stock			27,136	27	134,973		135,000
Expense related to stock warrants issued					212,000		212,000
Net loss						(1,055,485)	(1,055,485)
Balances at December 31, 1999 (unaudited)			234,399	234	2,769,161	(4,003,138)	(1,233,743)
Sale of preferred stock, net of offering costs of $76,500	3,200	32			3,123,468		3,123,500
Issuance of common stock			16,499	16	492,481		492,497

at conversion of notes and interest payable							
Issuance of common stock at conversion of notes payable			2,814	3	83,997		84,000
Issuance of common stock to settle obligations			19,804	20	1,202,140		1,202,160
Issuance of common stock for acquisition			280,000	280	9,332,489		9,332,769
Issuance of warrants for acquisition					4,767,664		4,767,664
Stock issued for acquisition costs			6,000	6	487,494		487,500
Expense related to stock warrants issued					140,000		140,000
Dividends payable on preferred stock					(85,000)		(85,000)
Cashless exercise of warrants			23,963	24	(24)		
Net loss						(3,701,084)	(3,701,084)
Balances at December 31, 2000 (unaudited)	3,200	32	583,479	583	22,313,870	(7,704,222)	14,610,263

See accompanying notes to consolidated financial statements.

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Mast Therapeutics, Inc. and Subsidiaries

(A Development Stage Enterprise)

Consolidated Statements of Stockholders Equity (Deficit)

Inception (June 12, 1996) Through December 31, 2013

	Cumulative convertible preferred stock, series A through C		Cumulative convertible preferred stock, series A (2009)		Cumulative convertible preferred stock, series B through F (2009 - 2010)		Common stock				Deficit accumulated during development stage	Treasury stock, at cost	Total stockholders equity (deficit)
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount	Additional paid-in capital	Accumulated other comprehensive income (loss)			
Dividends payable on preferred stock	$	$		$		$			$ (256,000)	$		$	$ (256,000)
Repurchase of warrants									(55,279)				(55,279)
Sale of warrants									47,741				47,741
Cashless exercise of warrants							8,740	9	(9)				
Issuance of common stock to pay preferred dividends							3,737	4	212,996				213,000
Detachable warrants issued with notes payable									450,000				450,000
Issuance of warrants to pay operating expenses									167,138				167,138
Issuance of common stock to pay							4,252	4	387,267				387,271

operating expenses							
Issuance of preferred stock to pay operating expenses	137	1			136,499		136,500
Net loss						(16,339,120)	(16,339,120)
Balances at December 31, 2001 (unaudited)	3,337	33	600,208	600	23,404,223	(24,043,342)	(638,486)
Dividends payable on preferred stock					(242,400)		(242,400)
Repurchase of warrants							
Sale of warrants			9,600	10	117,843		117,853
Cashless exercise of warrants							