

Mast Therapeutics, Inc.
Form S-3
March 24, 2015
Table of Contents

As filed with the Securities and Exchange Commission on March 24, 2015

Registration No. 333-

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

Mast Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

84-1318182
(I.R.S. employer
identification number)

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

3611 Valley Centre Drive, Suite 500

San Diego, CA 92130

(858) 552-0866

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Brandi L. Roberts

Chief Financial Officer and Senior Vice President

Mast Therapeutics, Inc.

3611 Valley Centre Drive, Suite 500

San Diego, CA 92130

(858) 552-0866

(Name, address, including zip code, and telephone number, including area code, of agent for service)

With Copies to:

Michael S. Kagnoff

DLA Piper LLP (US)

4365 Executive Drive, Ste 1100

San Diego, CA 92121

Tel: (858) 677-1400

Fax: (858) 677-1401

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of the registration statement.

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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 (Do not check if a smaller reporting company)

Smaller reporting company

Table of Contents**CALCULATION OF REGISTRATION FEE**

Title of Each Class of Securities to be Registered	Amount to be Registered(1)	Proposed Maximum Offering Price Per Share	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee
Common Stock, par value \$0.001 per share, issuable upon exercise of outstanding warrants	13,081,428(2)	\$0.01	\$130,814	
Common Stock, par value \$0.001 per share, issuable upon exercise of outstanding warrants	22,011,265(3)	\$0.75	\$16,508,449	
Common Stock, par value \$0.001 per share	(4)	(5)	(5)	
Preferred Stock, par value \$0.001 per share	(4)	(5)	(5)	
Debt Securities	(4)	(5)	(5)	
Warrants	(4)	(5)	(5)	
Units	(4)	(5)	(5)	
Total	(4)		\$166,639,263	\$19,364(6)

- (1) Pursuant to Rule 416 under the Securities Act of 1933, as amended (the Securities Act), the shares being registered hereunder include such indeterminate number of shares of common stock and preferred stock as may be issuable with respect to the shares being registered hereunder as a result of stock splits, stock dividends or similar transactions.
- (2) Consists of shares of common stock issuable upon the exercise of outstanding warrants with an exercise price of \$0.01 per share. Such warrants were issued and sold under the Prior Registration Statement (see footnote 6 below).
- (3) Consists of shares of common stock issuable upon the exercise of outstanding warrants with an exercise price of \$0.75 per share. Such warrants were issued and sold under the Prior Registration Statement (see footnote 6 below).
- (4) In addition to the shares of common stock issuable upon the exercise of outstanding warrants described in footnotes (1) and (2) above (collectively, the Warrant Shares), there are being registered hereunder such indeterminate number of shares of common stock, such indeterminate number of shares of preferred stock, such indeterminate principal amount of debt securities, and such indeterminate number of warrants to purchase common stock, preferred stock or debt securities as will have an aggregate initial offering price not to exceed \$150,000,000. If any debt securities are issued at an original issue discount, then the offering price of such debt securities shall be in such greater principal amount as shall result in an aggregate initial offering price not to exceed \$150,000,000, less the aggregate dollar amount of all securities previously issued hereunder. Any securities registered hereunder may be sold separately or as units with other securities registered hereunder. The securities registered also include such indeterminate number of shares of common stock and preferred stock and amount of debt securities as may be issued upon conversion of or exchange for preferred stock or debt securities that provide for conversion or exchange, upon exercise of warrants or pursuant to the antidilution provisions of any such securities.
- (5) The proposed maximum initial offering price per share and the proposed maximum aggregate offering price per class of security will be determined, from time to time, by the registrant in connection with the issuance by the registrant of the securities registered hereunder and is not specified as to each class of security pursuant to General Instruction II.D of Form S-3.
- (6)

Pursuant to Rule 415(a)(6) under the Securities Act, the securities registered hereunder include unsold securities previously registered pursuant to Registration Statement No. 333-179989, which was declared effective on May 1, 2012 (the Prior Registration Statement). The Prior Registration Statement registered the offer and sale of an indeterminate number of shares of common stock, an indeterminate number of shares of preferred stock, an indeterminate principal amount of debt securities, and an indeterminate number of warrants to purchase common stock, preferred stock or debt securities (collectively, the Shelf Securities) having an aggregate initial offering price not to exceed \$150,000,000, \$113,651,206.88 of which Shelf Securities remain unsold as the date of filing of this registration statement. The registrant has determined to include in this registration statement unsold Shelf Securities under the Prior Registration Statement with an aggregate offering price of \$113,651,206.88 (the Unsold Securities), which includes the aggregate offering price of \$16,639,263 with respect to the Warrant Shares as reflected in the table above. Pursuant to Rule 415(a)(6) under the Securities Act, the filing fee of \$13,024.43 relating to the Unsold Securities under the Prior Registration Statement, which was paid under the Prior Registration Statement, will continue to be applied to the Unsold Securities registered pursuant to this registration statement. The registrant is also registering new shelf securities on this registration statement with an aggregate initial offering price of \$52,988,056.15 (the New Securities), which aggregate offering price is not specified as to each class of security. To the extent that, after the filing date hereof and prior to the effectiveness of this registration statement, the registrant sells any Unsold Securities pursuant to the Prior Registration Statement, the Registrant will identify in a pre-effective amendment to this registration statement the updated amount of Unsold Securities from the Prior Registration Statement to be included in this registration statement pursuant to Rule 415(a)(6) and the updated amount of New Securities to be registered on this registration statement. Pursuant to Rule 415(a)(6), the offering of the Unsold Securities under the Prior Registration Statement will be deemed terminated as of the date of effectiveness of this registration statement. The filing fee of \$13,024.43 relating to the Unsold Securities under the Prior Registration Statement, which was paid under the Prior Registration Statement, will continue to be applied to the Unsold Securities registered pursuant to this registration statement. A filing fee of \$6,157.21 with respect to the New Securities is being paid in connection with the filing of this registration statement.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment that specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until this registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

Table of Contents

Explanatory Note

This registration statement contains three prospectuses:

a base prospectus which covers the offering, issuance and sale of such indeterminate number of shares of common stock and preferred stock, such indeterminate principal amount of debt securities, and such indeterminate number of warrants to purchase common stock, preferred stock or debt securities, which together shall have an aggregate initial offering price not to exceed \$150,000,000;

an at the market offering prospectus covering the offering, issuance and sale of shares of our common stock with an aggregate offering price of up to \$14,651,207 that may be issued and sold under a sales agreement we entered into with Cowen and Company, LLC, dated February 10, 2014, as amended from time to time; and

a warrant exercise offering prospectus covering the offering, issuance and sale of 35,092,693 shares of our common stock pursuant to the exercise of warrants to purchase shares of our common stock outstanding on March 24, 2015.

The base prospectus immediately follows this explanatory note. The specific terms of any securities to be offered pursuant to the base prospectus will be specified in a prospectus supplement to the base prospectus. The at the market offering prospectus immediately follows the base prospectus. The shares of common stock that may be offered, issued and sold under the at the market offering prospectus is included in the \$150,000,000 of securities that may be offered, issued and sold under the base prospectus. In the event of the termination of the sales agreement, any portion of the \$14,651,207 included in the at the market offering prospectus that is not sold pursuant to the sales agreement will be available for sale in other offerings pursuant to the base prospectus. The warrant exercise offering prospectus immediately follows the at the market offering prospectus.

Table of Contents

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MARCH 24, 2015

PROSPECTUS

\$150,000,000

Common Stock

Preferred Stock

Debt Securities

Warrants

Units

We may, from time to time in one or more offerings, offer and sell up to \$150,000,000 in the aggregate of common stock, preferred stock, debt securities, warrants to purchase common stock, preferred stock or debt securities, or any combination of the foregoing, either individually or as units comprised of one or more of the other securities.

This prospectus provides a general description of the securities we may offer. We will provide the specific terms of the securities offered in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may add, update or change information contained in this prospectus. You should read carefully this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as the documents incorporated by reference before you invest in any of our securities. **This prospectus may not be used to offer or sell any securities unless accompanied by the applicable prospectus supplement.**

Our common stock is listed on the NYSE MKT under the symbol MSTX. On March 23, 2015, the last reported sale price for our common stock was \$0.52 per share.

Investing in our securities involves a high degree of risk. See Risk Factors on page 5 of this prospectus and in the documents incorporated by reference in this prospectus, as updated in the applicable prospectus supplement, any related free writing prospectus and other future filings we make with the Securities and Exchange Commission that are incorporated by reference into this prospectus, for a discussion of the factors you should consider carefully before deciding to purchase our securities.

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

We will sell these securities directly to investors, through agents designated from time to time or to or through underwriters or dealers. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus. If any underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters and any applicable commissions or discounts will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is _____, 2015

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	ii
<u>SUMMARY</u>	1
<u>RISK FACTORS</u>	5
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	5
<u>USE OF PROCEEDS</u>	6
<u>SECURITIES WE MAY OFFER</u>	6
<u>DESCRIPTION OF COMMON STOCK AND PREFERRED STOCK</u>	6
<u>DESCRIPTION OF DEBT SECURITIES</u>	10
<u>DESCRIPTION OF WARRANTS</u>	18
<u>DESCRIPTION OF UNITS</u>	20
<u>LEGAL OWNERSHIP OF SECURITIES</u>	21
<u>PLAN OF DISTRIBUTION</u>	24
<u>LEGAL MATTERS</u>	26
<u>EXPERTS</u>	26
<u>INFORMATION INCORPORATED BY REFERENCE</u>	26
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	27

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, under the Securities Act of 1933, as amended, or the Securities Act, using a shelf registration process. Under this shelf registration process, we may from time to time sell common stock, preferred stock, debt securities or warrants to purchase common stock, preferred stock or debt securities, or any combination of the foregoing, either individually or as units comprised of one or more of the other securities, in one or more offerings up to a total dollar amount of \$150,000,000. We have provided to you in this prospectus a general description of the securities we may offer. Each time we sell securities under this shelf registration, we will, to the extent required by law, provide a prospectus supplement that will contain specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in any documents that we have incorporated by reference into this prospectus. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement or any related free writing prospectus, you should rely on the information in the prospectus supplement or the related free writing prospectus; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document filed after the date of this prospectus and incorporated by reference into this prospectus or any prospectus supplement or any related free writing perspective—the statement in the document having the later date modifies or supersedes the earlier statement.

We have not authorized any dealer, agent or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement, or any related free writing prospectus that we may authorize to be provided to you. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus or an accompanying prospectus supplement, or any related free writing prospectus that we may authorize to be provided to you. This prospectus and the accompanying prospectus supplement, if any, do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus and the accompanying prospectus supplement constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference (as our business, financial condition, results of operations and prospects may have changed since that date), even though this prospectus, any applicable prospectus supplement or any related free writing prospectus is delivered or securities are sold on a later date.

As permitted by SEC rules and regulations, the registration statement of which this prospectus forms a part includes additional information not contained in this prospectus. You may read the registration statement and the other reports we file with the SEC at its web site or at its offices described below under **Where You Can Find More Information**.

Table of Contents

SUMMARY

This summary highlights the information contained elsewhere in or incorporated by reference into this prospectus. Because this is only a summary, it does not contain all of the information that you should consider before investing in our securities. You should carefully read this entire prospectus, including the information contained under the heading Risk Factors, and all other information included or incorporated by reference into this prospectus in their entirety before you invest in our securities.

Unless the context otherwise requires, all references in this prospectus to Mast, we, us, our, the Company or similar words refer to Mast Therapeutics, Inc., together with our consolidated subsidiaries.

Company Overview

We are a clinical-stage, biopharmaceutical company developing novel therapies for serious or life-threatening diseases with significant unmet needs. We are leveraging our Molecular Adhesion & Sealant Technology, or MAST, platform, derived from over two decades of clinical, nonclinical, and manufacturing experience with purified and non-purified poloxamers, to develop MST-188 (vepoloxamer) Injection, our lead product candidate. Vepoloxamer has demonstrated multiple pharmacologic effects that may provide clinical benefit in a wide range of diseases and conditions typically characterized by impaired microvascular blood flow and/or damaged cell membranes. We currently are developing vepoloxamer for the treatment of sickle cell disease, arterial disease (in combination with thrombolytics), and heart failure. We also are developing AIR001, a sodium nitrite solution for intermittent inhalation via nebulizer. AIR001 has demonstrated positive hemodynamic effects in patients with pulmonary hypertension and we are developing it for the treatment of heart failure with preserved ejection fraction, or HFpEF.

We have devoted substantially all of our resources to research and development and to acquisition of our product candidates. We have not yet marketed or sold any products or generated any significant revenue and we have incurred significant annual operating losses since inception. We incurred losses from operations of \$29.3 million and \$21.5 million for the years ended December 31, 2014 and December 31, 2013, respectively. As of December 31, 2014, we had an accumulated deficit of \$235.1 million. Our cash, cash equivalents, and investment securities were \$57.3 million as of December 31, 2014.

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

Our second product candidate, AIR001, is being tested in multiple institution-sponsored Phase 2a clinical studies in patients with HFpEF. We obtained the AIR001 program through our acquisition of Aires Pharmaceuticals, Inc. in February 2014. Prior to the acquisition, AIR001 had been tested in more than 120 healthy volunteers and patients with various forms of pulmonary hypertension and it demonstrated positive hemodynamic effects and was well-tolerated. If data from the Phase 2a studies are positive, we expect to conduct a Phase 2b proof-of-concept study in HFpEF.

Table of Contents

Corporate Information

In March 2013, we changed our name from ADVENTRX Pharmaceuticals, Inc. to Mast Therapeutics, Inc.

Our principal executive offices are located at 3611 Valley Centre Drive, Suite 500, San Diego, CA 92130 and our telephone number at that address is (858) 552-0866. Our corporate website is located at www.masttherapeutics.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and 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, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The information contained in, or that can be accessed through, our website is not part of this prospectus or any prospectus supplement.

The Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and warrants to purchase any of such securities, either individually or in units, with a total value of up to \$150,000,000 from time to time under this prospectus, together with any applicable prospectus supplement and related free writing prospectus, at prices and on terms to be determined by market conditions at the time of offering. If we issue any debt securities at a discount from their original stated principal amount, then, for purposes of calculating the total dollar amount of all securities issued under this prospectus, we will treat the initial offering price of the debt securities as the total original principal amount of the debt securities. Each time we offer securities under this prospectus, we will provide offerees with a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities being offered, including, to the extent applicable:

designation or classification;

aggregate principal amount or aggregate offering price;

maturity, if applicable;

original issue discount, if any;

rates and times of payment of interest or dividends, if any;

redemption, conversion, exchange or sinking fund terms, if any;

conversion or exchange prices or rates, if any, and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange;

ranking;

restrictive covenants, if any;

voting or other rights, if any; and

important United States federal income tax considerations.

The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

Table of Contents

We may sell the securities to or through underwriters, dealers or agents or directly to purchasers. We, as well as any agents acting on our behalf, reserve the sole right to accept and to reject in whole or in part any proposed purchase of securities. Each prospectus supplement will set forth the names of any underwriters, dealers or agents involved in the sale of securities described in that prospectus supplement and any applicable fee, commission or discount arrangements with them, details regarding any over-allotment option granted to them, and net proceeds to us. The following is a summary of the securities we may offer with this prospectus.

Common Stock

As of the date of this prospectus, our amended and restated certificate of incorporation, as amended, or our certificate of incorporation, authorizes us to issue 500,000,000 shares of common stock, par value \$0.001 per share, of which 159,458,376 shares were issued and outstanding as of March 20, 2015. We may offer shares of our common stock either alone or underlying other registered securities convertible into or exercisable for our common stock. Holders of our common stock are entitled to such dividends as our board of directors may declare from time to time out of legally available funds, subject to the preferential rights of the holders of any shares of our preferred stock that are outstanding or that we may issue in the future. Currently, we do not pay any dividends on our common stock. Each holder of our common stock is entitled to one vote per share. In this prospectus, we provide a general description of, among other things, the rights and restrictions that apply to holders of our common stock.

Preferred Stock

As of the date of this prospectus, our certificate of incorporation authorizes us to issue 1,000,000 shares of preferred stock, par value \$0.001 per share, none of which are outstanding. We may issue shares of our preferred stock from time to time, in one or more series.

Any authorized and undesignated shares of preferred stock may be issued with such rights and powers as the board of directors may designate. Under our certificate of incorporation, our board of directors has the authority to issue shares of our preferred stock in one or more series and to fix or alter the rights, preferences, privileges and restrictions granted to or imposed upon any series of preferred stock. The particular terms of each class or series of preferred stock, including redemption privileges, liquidation preferences, voting rights, dividend rights and/or conversion rights, will be more fully described in the applicable prospectus supplement relating to the preferred stock offered thereby.

The rights, preferences, privileges and restrictions granted to or imposed upon any series of preferred stock that we offer and sell under this prospectus and applicable prospectus supplements will be set forth in a certificate of designation relating to the series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of any certificate of designation that describes the terms of any series of preferred stock we offer under this prospectus before the issuance of shares of that series of preferred stock. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities

We may offer general debt obligations, which may be secured or unsecured, senior or subordinated and convertible into shares of our common stock. In this prospectus, we refer to the senior debt securities and the subordinated debt securities together as the debt securities. We may issue debt securities under a note purchase agreement or under an indenture to be entered between us and a trustee; forms of the senior and subordinated

Table of Contents

indentures are included as an exhibit to the registration statement of which this prospectus is a part. The indentures do not limit the amount of securities that may be issued under it and provides that debt securities may be issued in one or more series. The senior debt securities will have the same rank as all of our other indebtedness that is not subordinated. The subordinated debt securities will be subordinated to our senior debt on terms set forth in the applicable prospectus supplement. In addition, the subordinated debt securities will be effectively subordinated to creditors and preferred stockholders of our subsidiaries. Our board of directors will determine the terms of each series of debt securities being offered. This prospectus contains only general terms and provisions of the debt securities. The applicable prospectus supplement will describe the particular terms of the debt securities offered thereby. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of debt securities being offered, as well as the complete note agreements and/or indentures that contain the terms of the debt securities. Forms of indentures have been filed as exhibits to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of debt securities we offer under this prospectus will be filed as exhibits to the registration statement of which this prospectus is a part, or will be incorporated by reference from another report that we file with the SEC.

Warrants

We may offer warrants for the purchase of shares of our common stock or preferred stock or of debt securities. We may issue the warrants by themselves or together with common stock, preferred stock or debt securities, and the warrants may be attached to or separate from any offered securities. Our board of directors will determine the terms of the warrants. This prospectus contains only general terms and provisions of the warrants. The applicable prospectus supplement will describe the particular terms of the warrants being offered thereby. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of warrants being offered, as well as the complete form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the warrants. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants.

Units

We may offer units consisting of our common stock or preferred stock, debt securities and/or warrants to purchase any of these securities in one or more series. We may evidence each series of units by unit certificates that we will issue under a separate agreement. We may enter into unit agreements with a unit agent. Each unit agent will be a bank or trust company that we select. We will indicate the name and address of the unit agent in the applicable prospectus supplement relating to a particular series of units. This prospectus contains only a summary of certain general features of the units. The applicable prospectus supplement will describe the particular features of the units being offered thereby. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of units being offered, as well as the complete unit agreements that contain the terms of the units. Specific unit agreements will contain additional important terms and provisions and we will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of each unit agreement relating to units offered under this prospectus.

Table of Contents

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider the risk factors set forth under Risk Factors in Item 1A of our annual report on Form 10-K for the year ended December 31, 2014, which is incorporated by reference in this prospectus, together with all other information contained or incorporated by reference in this prospectus, as may be updated by our subsequent filings under the Exchange Act, and the risk factors and other information contained in any applicable prospectus supplement and in any related free writing prospectus in connection with a specific offering, before deciding whether to purchase any of the securities being registered pursuant to the registration statement of which this prospectus is a part. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Additional risks and uncertainties that we do not presently know about or that we currently believe are not material may also adversely affect our business.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and our SEC filings that are incorporated by reference into this prospectus contain or incorporate by reference forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. All statements, other than statements of historical fact, included or incorporated by reference in this prospectus regarding our development of our products, financial position, strategy, regulatory status, clinical and nonclinical studies, collaborations, commercial prospects, internal growth, competition, intellectual property, regulatory reforms, products, objectives of management, and compliance with NYSE MKT listing standards are forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

the initiation, scope, rate of progress, results and timing of our clinical and nonclinical studies of

our product candidates, including vepoloxamer;

the successful completion of our development programs and our ability to manage costs associated with clinical and nonclinical development of our product candidates, including vepoloxamer;

our ability to obtain and maintain regulatory approvals of our product candidates, including vepoloxamer;

our ability to commercialize and achieve market acceptance of our product candidates, including vepoloxamer;

our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others;

our estimates regarding the sufficiency of our cash resources and our need for additional funding; and

our intended use of the net proceeds from offerings of our securities under this prospectus. The words believe, anticipate, estimate, plan, expect, intend, may, could, should, potential, will, and would and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements reflect our current views with respect to future events, are based on assumptions and are subject to risks and uncertainties. We cannot guarantee that we actually will achieve the plans, intentions or expectations expressed in our forward-looking statements and you should not place undue reliance on these statements. There are a number of important factors that could cause our actual results to differ materially from those indicated or implied by forward-looking statements. These important factors include those discussed under the heading Risk Factors contained or incorporated in this prospectus and in the applicable prospectus supplement and any free writing prospectus we may authorize for use in connection with a specific offering.

Table of Contents

These factors and the other cautionary statements made in this prospectus should be read as being applicable to all related forward-looking statements whenever they appear in this prospectus. Except as required by law, we do not assume any obligation to update any forward-looking statement. We disclaim any intention or obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

USE OF PROCEEDS

Except as described in any prospectus supplement and any free writing prospectus in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered under this prospectus to fund continued development of our product candidates, including clinical studies, nonclinical testing and research-related manufacturing activities, to pursue regulatory approval for our product candidates and, potentially, to commercialize product candidates that receive regulatory approval, and for general corporate purposes, including working capital. We may also use a portion of the net proceeds to acquire or invest in technologies, product candidates, products and/or businesses that we believe will enhance the value of our company, although we have no current commitments or agreements with respect to any such transactions as of the date of this prospectus. We have not determined the amount of net proceeds to be used specifically for the foregoing purposes. As a result, our management will have broad discretion in the allocation of the net proceeds and investors will be relying on the judgment of our management regarding the application of the proceeds of any sale of the securities. If a material part of the net proceeds is to be used to repay indebtedness, we will set forth the interest rate and maturity of such indebtedness in a prospectus supplement. Pending use of the net proceeds, we intend to invest the proceeds in interest-bearing, marketable securities.

SECURITIES WE MAY OFFER

We may offer shares of common stock, shares of preferred stock, debt securities or warrants to purchase common stock, preferred stock or debt securities, or any combination of the foregoing, either individually or as units comprised of one or more of the other securities. We may offer up to \$150,000,000 of securities under this prospectus. If securities are offered as units, we will describe the terms of the units in a prospectus supplement.

DESCRIPTION OF COMMON STOCK AND PREFERRED STOCK

The following description of our common stock and preferred stock, together with any additional information we include in any applicable prospectus supplement or any related free writing prospectus, summarizes the material terms and provisions of our common stock and the preferred stock that we may offer under this prospectus. While the terms we have summarized below will apply generally to any future common stock or preferred stock that we may offer, we will describe the particular terms of any class or series of these securities in more detail in the applicable prospectus supplement. For the complete terms of our common stock and preferred stock, please refer to our certificate of incorporation and our bylaws, each as amended to date, that are incorporated by reference into the registration statement of which this prospectus is a part or may be incorporated by reference in this prospectus or any applicable prospectus supplement. The terms of these securities may also be affected by the Delaware General Corporation Law, or the DGCL. The summary below and that contained in any applicable prospectus supplement or any related free writing prospectus are qualified in their entirety by reference to our certificate of incorporation and bylaws, as in effect at the time of any offering of securities under this prospectus.

Table of Contents

Common Stock

As of the date of this prospectus, our certificate of incorporation authorizes us to issue 500,000,000 shares of common stock, par value \$0.001 per share, of which 159,458,376 shares were issued and outstanding as of March 20, 2015. Additional shares of authorized common stock may be issued, as authorized by our board of directors from time to time, without stockholder approval, except as may be required by applicable securities exchange requirements. The holders of common stock possess exclusive voting rights in us, except to the extent our board of directors specifies voting power with respect to any other class of securities issued in the future. Each holder of our common stock is entitled to one vote for each share held of record on each matter submitted to a vote of stockholders, including the election of directors. Stockholders do not have any right to cumulate votes in the election of directors.

Subject to preferences that may be granted to the holders of preferred stock, each holder of our common stock is entitled to share ratably in distributions to stockholders and to receive ratably such dividends as may be declared by our board of directors out of funds legally available therefor. In the event of our liquidation, dissolution or winding up, the holders of our common stock will be entitled to receive, after payment of all of our debts and liabilities and of all sums to which holders of any preferred stock may be entitled, the distribution of any of our remaining assets. Holders of our common stock have no conversion, exchange, sinking fund or redemption rights and have no preemptive rights to subscribe for any of our securities.

All of the outstanding shares of our common stock are fully paid and non-assessable. The shares of common stock offered by this prospectus or upon the conversion of any preferred stock or debt securities or exercise of any warrants offered pursuant to this prospectus, when issued and paid for, will also be, fully paid and non-assessable.

Securities Exchange Listing

Our common stock is listed on the NYSE MKT under the symbol MSTX.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company.

Preferred Stock

As of the date of this prospectus, our certificate of incorporation authorizes us to issue 1,000,000 shares of preferred stock, par value \$0.001 per share, none of which are outstanding. Pursuant to our certificate of incorporation, our board of directors has the authority to provide for the issuance, in one or more series, of our authorized preferred stock and to fix or alter the rights, preferences, privileges and restrictions granted to or imposed upon any series of our preferred stock. The rights, privileges, preferences and restrictions of any such series of our preferred stock may be subordinated to, pari passu with (including, without limitation, inclusion in provisions with respect to liquidation and acquisition preferences, redemption or approval of matters by vote or written consent), or senior to any of those of any present or future class or series of preferred stock or common stock. Our board of directors is also expressly authorized to increase or decrease the number of shares of any series prior or subsequent to the issue of that series, but not below the number of shares of such series then outstanding. The issuance of preferred stock may have the effect of decreasing the market price of our common stock and may adversely affect the voting power of holders of our common stock and reduce the likelihood that holders of our common stock will receive dividend payments and payments upon liquidation.

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

The particular terms of each class or series of preferred stock that we may offer under this prospectus, including redemption privileges, liquidation preferences, voting rights, dividend rights and/or conversion rights, will be more fully described in the applicable prospectus supplement relating to the preferred stock offered

Table of Contents

thereby. The rights, preferences, privileges and restrictions of any series of preferred stock that we may offer under this prospectus will be set forth in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we may offer before the issuance of the related series of preferred stock. The applicable prospectus supplement will specify the terms of the series of preferred stock we may offer, including, but not limited to:

the distinctive designation and the maximum number of shares in the series;

the number of shares we are offering and purchase price per share;

the liquidation preference, if any;

the terms on which dividends, if any, will be paid;

the voting rights, if any, of the shares of the series;

the terms and conditions, if any, on which the shares of the series shall be convertible into, or exchangeable for, shares of any other class or classes of capital stock;

the terms on which the shares may be redeemed, if at all;

any listing of the preferred stock on any securities exchange or market;

a discussion of any material or special United States federal income tax considerations applicable to the preferred stock; and

any or all other preferences, rights, restrictions, including restrictions on transferability, and qualifications of shares of the series.

The description of preferred stock above and the description of the terms of a particular series of preferred stock in any applicable prospectus supplement are not complete. You should refer to the applicable certificate of designation for complete information.

The DGCL provides that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of that preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

Anti-Takeover Effects of Provisions of our Charter Documents and Delaware Law

Provisions of the DGCL, our certificate of incorporation and our bylaws could make it more difficult to acquire us by means of a tender offer, a proxy contest or otherwise, or to remove incumbent officers and directors. These provisions, summarized below, are expected to discourage certain types of coercive takeover practices and takeover bids that our board of directors may consider inadequate and to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of increased protection of our ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging takeover or acquisition proposals because, among other things, negotiation of these proposals could result in an improvement of their terms. This summary does not purport to be complete and is qualified in its entirety by reference to the DGCL and our certificate of incorporation and bylaws.

Certificate of Incorporation and Bylaws

Preferred Stock. Under our certificate of incorporation, our board of directors has the power to authorize the issuance of up to 1,000,000 shares of preferred stock, all of which are currently undesignated, and to determine

Table of Contents

the price, rights, preferences, privileges and restrictions, including voting rights, of those shares without further vote or action by our stockholders. The issuance of preferred stock may:

delay, defer or prevent a change in control;

discourage bids for our common stock at a premium over the market price of our common stock;

adversely affect the voting and other rights of the holders of our common stock; and

discourage acquisition proposals or tender offers for our shares and, as a consequence, inhibit fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Advance Notice Requirement. Stockholder nominations of individuals for election to our board of directors and stockholder proposals of other matters to be brought before an annual meeting of our stockholders must comply with the advance notice procedures set forth in our bylaws. Generally, to be timely, such notice must be received at our principal executive offices no later than the date specified in our proxy statement released to stockholders in connection with the preceding year's annual meeting of stockholders, which date shall be not earlier than the 120th day, nor later than the close of business on the 90th day, prior to the first anniversary of the date of the preceding year's annual meeting of stockholders.

Special Meeting Requirements. Our bylaws provide that special meetings of our stockholders may be called only at the request of our board of directors, president (unless there is a chief executive officer who is not the president, in which case a special meeting may be called at any time by the chief executive officer and not the president) or chair of the board of directors. Only such business shall be considered at a special meeting as shall have been stated in the notice for such meeting.

No Cumulative Voting. Our certificate of incorporation does not include a provision for cumulative voting for directors.

Indemnification. Our certificate of incorporation and bylaws provide that we will indemnify our officers and directors against losses as they incur in investigations and legal proceedings resulting from their services to us, which may include service in connection with takeover defense measures.

Removal of Directors. Our bylaws provide that the affirmative vote of the holders of at least 75% of our voting stock then outstanding is required to remove our directors, either with or without cause.

Authorized but Unissued Shares. Our authorized but unissued shares of common stock and preferred stock will be available for future issuance without stockholder approval. We may use additional shares for a variety of purposes, including future public offerings to raise additional capital, to fund acquisitions and as employee compensation. The existence of authorized but unissued shares of common stock and preferred stock could render more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

Delaware Anti-Takeover Statute

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

We are subject to Section 203 of the DGCL, an anti-takeover law. In general, Section 203 prohibits, with some exceptions, a publicly held Delaware corporation from engaging in a business combination with any interested stockholder for a period of three years following the date that stockholder became an interested stockholder, unless:

prior to that date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

Table of Contents

upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares of voting stock outstanding (but not the voting stock owned by the interested stockholder) those shares owned by persons who are directors and officers and by excluding employee stock plans in which employee participants do not have the right to determine whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to that date, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66-2/3% of the outstanding voting stock that is not owned by the interested stockholder.

Section 203 defines "business combination" to include any of the following:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an "interested stockholder" as any person who, together with the person's affiliates and associates, beneficially owns, or within three years prior to the determination of interested stockholder status did beneficially own, 15% or more of the outstanding voting stock of the corporation.

The above provisions may deter a hostile takeover or delay a change in control of management or us.

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. The following description, together with the additional information we include in any applicable prospectus supplements or free writing prospectuses, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus. While the terms we have summarized below will apply generally to any future debt securities we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement or free writing prospectus. The

terms of any debt securities we offer under a prospectus supplement may differ from the terms we describe below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. As of March 24, 2015, we have no outstanding registered debt securities. Unless the context requires otherwise, whenever we refer to the indentures, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue any senior debt securities under the senior indenture that we will enter into with the trustee named in the senior indenture. We will issue any subordinated debt securities under the subordinated indenture and any supplemental indentures that we will enter into with the trustee named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, of which this prospectus is a part,

Table of Contents

and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The indentures will be qualified under the Trust Indenture Act of 1939, as amended (the Trust Indenture Act). We use the term trustee to refer to either the trustee under the senior indenture or the trustee under the subordinated indenture, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all of the provisions of the indenture and any supplemental indentures applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indentures that contains the terms of the debt securities. Except as we may otherwise indicate, the terms of the senior indenture and the subordinated indenture are identical.

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors and set forth or determined in the manner provided in an officers certificate or by a supplemental indenture. Debt securities may be issued in separate series without limitation as to aggregate principal amount. We may specify a maximum aggregate principal amount for the debt securities of any series. We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

the title;

the principal amount being offered, and if a series, the total amount authorized and the total amount outstanding;

any limit on the amount that may be issued;

whether or not we will issue the series of debt securities in global form, and, if so, the terms and who the depositary will be;

the maturity date;

whether and under what circumstances, if any, we will pay additional amounts on any debt securities held by a person who is not a United States person for tax purposes, and whether we can redeem the debt securities if we have to pay such additional amounts;

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

the annual interest rate, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;

whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

the terms of the subordination of any series of subordinated debt;

the place where payments will be made;

restrictions on transfer, sale or other assignment, if any;

our right, if any, to defer payment of interest and the maximum length of any such deferral period;

the date, if any, after which, and the price at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;

Table of Contents

provisions for a sinking fund purchase or other analogous fund, if any, including the date, if any, on which, and the price at which we are obligated, pursuant thereto or otherwise, to redeem, or at the holder's option, to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;

whether the indenture will restrict our ability or the ability of our subsidiaries to:

incur additional indebtedness;

issue additional securities;

create liens;

pay dividends or make distributions in respect of our capital stock or the capital stock of our subsidiaries;

redeem capital stock;

place restrictions on our subsidiaries' ability to pay dividends, make distributions or transfer assets;

make investments or other restricted payments;

sell or otherwise dispose of assets;

enter into sale-leaseback transactions;

engage in transactions with stockholders or affiliates;

issue or sell stock of our subsidiaries; or

effect a consolidation or merger;

whether the indenture will require us to maintain any interest coverage, fixed charge, cash flow-based, asset-based or other financial ratios;

a discussion of certain material or special United States federal income tax considerations applicable to the debt securities;

information describing any book-entry features;

the applicability of the provisions in the indenture on discharge;

whether the debt securities are to be offered at a price such that they will be deemed to be offered at an original issue discount as defined in paragraph (a) of Section 1273 of the Internal Revenue Code of 1986, as amended;

the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof;

the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars; and

any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, including any additional events of default or covenants provided with respect to the debt securities, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement the terms under which a series of debt securities may be convertible into or exchangeable for our common stock, our preferred stock or other securities (including securities of a third party). We will include provisions as to whether conversion or exchange is mandatory, at the

Table of Contents

option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock, our preferred stock or other securities (including securities of a third party) that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indentures will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets must assume all of our obligations under the indentures or the debt securities, as appropriate. If the debt securities are convertible into or exchangeable for our other securities or securities of other entities, the person with whom we consolidate or merge or to whom we sell all of our property must make provisions for the conversion of the debt securities into securities that the holders of the debt securities would have received if they had converted the debt securities before the consolidation, merger or sale.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indentures with respect to any series of debt securities that we may issue:

if we fail to pay interest when due and payable and our failure continues for 90 days and the time for payment has not been extended;

if we fail to pay the principal, premium or sinking fund payment, if any, when due and payable at maturity, upon redemption or repurchase or otherwise, and the time for payment has not been extended;

if we fail to observe or perform any other covenant contained in the debt securities or the indentures, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive notice from the trustee or we and the trustee receive notice from the holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and

if specified events of bankruptcy, insolvency or reorganization occur.

We will describe in each applicable prospectus supplement any additional events of default relating to the relevant series of debt securities.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default arises due to the occurrence of certain specified bankruptcy, insolvency or reorganization events, the unpaid principal, premium, if any, and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indentures, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at

Table of Contents

the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity or security satisfactory to it against any loss, liability or expense. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

the direction so given by the holder is not in conflict with any law or the applicable indenture; and

subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

The indentures provide that if an event of default has occurred and is continuing, the trustee will be required in the exercise of its powers to use the degree of care that a prudent person would use in the conduct of its own affairs. The trustee, however, may refuse to follow any direction that conflicts with law or the indenture, or that the trustee determines is unduly prejudicial to the rights of any other holder of the relevant series of debt securities, or that would involve the trustee in personal liability. Prior to taking any action under the indentures, the trustee will be entitled to indemnification against all costs, expenses and liabilities that would be incurred by taking or not taking such action.

A holder of the debt securities of any series will have the right to institute a proceeding under the indentures or to appoint a receiver or trustee, or to seek other remedies only if:

the holder has given written notice to the trustee of a continuing event of default with respect to that series;

the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made a written request and such holders have offered reasonable indemnity to the trustee or security satisfactory to it against any loss, liability or expense or to be incurred in compliance with instituting the proceeding as trustee; and

the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities, or other defaults that may be specified in the applicable prospectus supplement.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indentures.

The indentures provide that if a default occurs and is continuing and is actually known to a responsible officer of the trustee, the trustee must mail to each holder notice of the default within the earlier of 90 days after it occurs and 30 days after it is known by a responsible officer of the trustee or written notice of it is received by the trustee, unless such default has been cured or waived. Except in the case of a default in the payment of principal or premium of, or

interest on, any debt security or certain other defaults specified in an indenture, the trustee shall be protected in withholding such notice if and so long as the board of directors, the executive committee or a trust committee of directors, or responsible officers of the trustee, in good faith determine that withholding notice is in the best interests of holders of the relevant series of debt securities.

Table of Contents

Modification of Indenture; Waiver

Subject to the terms of the indenture for any series of debt securities that we may issue, we and the trustee may change an indenture without the consent of any holders with respect to the following specific matters:

to fix any ambiguity, defect or inconsistency in the indenture;

to comply with the provisions described above under Description of Debt Securities Consolidation, Merger or Sale;

to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act;

to add to, delete from or revise the conditions, limitations and restrictions on the authorized amount, terms or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;

to provide for the issuance of, and establish the form and terms and conditions of, the debt securities of any series as provided under Description of Debt Securities General, to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;

to evidence and provide for the acceptance of appointment hereunder by a successor trustee;

to provide for uncertificated debt securities and to make all appropriate changes for such purpose;

to add such new covenants, restrictions, conditions or provisions for the benefit of the holders, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred to us in the indenture; or

to change anything that does not adversely affect the interests of any holder of debt securities of any series in any material respect.

In addition, under the indentures, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, subject to the terms of the indenture for any series of debt securities that we may issue or otherwise provided in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may only make the following changes with the consent of each holder of any outstanding debt securities affected:

extending the stated maturity of the series of debt securities;

reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption or repurchase of any debt securities; or

reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that, subject to the terms of the indenture and any limitation otherwise provided in the prospectus supplement applicable to a particular series of debt securities, we may elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

register the transfer or exchange of debt securities of the series;

replace stolen, lost or mutilated debt securities of the series;

maintain paying agencies;

Table of Contents

hold monies for payment in trust;

recover excess money held by the trustee;

compensate and indemnify the trustee; and

appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, and any premium and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indentures provide that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company or another depository named by us and identified in a prospectus supplement with respect to that series. See *Legal Ownership of Securities* below for a further description of the terms relating to any book-entry securities.

At the option of the holder, subject to the terms of the indentures and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indentures and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will make no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that

may be selected for redemption and ending at the close of business on the day of the mailing; or

register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture and is under no

Table of Contents

obligation to exercise any of the powers given it by the indentures at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur. However, upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest payment.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indentures and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act is applicable.

Ranking Debt Securities

The subordinated debt securities will be unsecured and will be subordinate and junior in priority of payment to certain other indebtedness to the extent described in a prospectus supplement. The subordinated indenture does not limit the amount of subordinated debt securities that we may issue. It also does not limit us from issuing any other secured or unsecured debt.

The senior debt securities will be unsecured and will rank equally in right of payment to all our other senior unsecured debt. The senior indenture does not limit the amount of senior debt securities that we may issue. It also does not limit us from issuing any other secured or unsecured debt.

Existing Subordinated Debt

As of December 31, 2014, we had no existing subordinated debt.

Table of Contents

DESCRIPTION OF WARRANTS

General

We may issue warrants for the purchase of common stock, preferred stock or debt securities. Warrants may be offered independently or together with common stock, preferred stock or debt securities offered by any prospectus supplement and may be attached to or separate from those securities. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe in particular the terms of any series of warrants that we may offer in more detail in the applicable prospectus supplement and any applicable free writing prospectus. The terms of any warrants offered under a prospectus supplement may differ from the terms described below.

We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report that we file with the SEC, the form of warrant and/or warrant agreement, which may include a form of warrant certificate, as applicable, that describes the terms of the particular series of warrants we may offer before the issuance of the related series of warrants. We may issue the warrants under a warrant agreement that we will enter into with a warrant agent to be selected by us. The warrant agent will act solely as our agent in connection with the warrants and will not assume any obligation or relationship of agency or trust for or with any registered holders of warrants or beneficial owners of warrants. The following summary of material provisions of the warrants and warrant agreements are subject to, and qualified in their entirety by reference to, all the provisions of the form of warrant and/or warrant agreement and warrant certificate applicable to a particular series of warrants. We urge you to read the applicable prospectus supplement and any related free writing prospectus, as well as the complete form of warrant and/or the warrant agreement and warrant certificate, as applicable, that contain the terms of the warrants.

The particular terms of any issue of warrants will be described in the prospectus supplement relating to the issue. Those terms may include:

the title of such warrants;

the aggregate number of such warrants;

the price or prices at which such warrants will be issued;

the currency or currencies (including composite currencies) in which the price of such warrants may be payable;

the terms of the securities purchasable upon exercise of such warrants and the procedures and conditions relating to the exercise of such warrants;

the price at which the securities purchasable upon exercise of such warrants may be purchased;

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

the date on which the right to exercise such warrants will commence and the date on which such right shall expire;

any provisions for adjustment of the number or amount of securities receivable upon exercise of the warrants or the exercise price of the warrants;

if applicable, the minimum or maximum amount of such warrants that may be exercised at any one time;

if applicable, the designation and terms of the securities with which such warrants are issued and the number of such warrants issued with each such security;

if applicable, the date on and after which such warrants and the related securities will be separately transferable;

Table of Contents

information with respect to book-entry procedures, if any;

the terms of any rights to redeem or call the warrants;

United States federal income tax consequences of holding or exercising the warrants, if material; and

any other terms of such warrants, including terms, procedures and limitations relating to the exchange or exercise of such warrants.

Each warrant will entitle its holder to purchase the principal amount of debt securities or the number of shares of preferred stock or common stock at the exercise price set forth in, or calculable as set forth in, the applicable prospectus supplement. The warrants may be exercised as set forth in the prospectus supplement relating to the warrants offered. Unless we otherwise specify in the applicable prospectus supplement, warrants may be exercised at any time up to the close of business on the expiration date set forth in the prospectus supplement relating to the warrants offered thereby. After the close of business on the expiration date, unexercised warrants will become void.

We will specify the place or places where, and the manner in which, warrants may be exercised in the form of warrant, warrant agreement or warrant certificate and applicable prospectus supplement. Upon receipt of payment and the warrant or warrant certificate, as applicable, properly completed and duly executed at the corporate trust office of the warrant agent, if any, or any other office, including ours, indicated in the prospectus supplement, we will, as soon as practicable, issue and deliver the securities purchasable upon such exercise. If less than all of the warrants (or the warrants represented by such warrant certificate) are exercised, a new warrant or a new warrant certificate, as applicable, will be issued for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Prior to the exercise of any warrants to purchase common stock, preferred stock or debt securities, holders of the warrants will not have any of the rights of holders of the common stock, preferred stock or debt securities purchasable upon exercise, including (i) in the case of warrants for the purchase of common stock or preferred stock, the right to vote or to receive any payments of dividends or payments upon our liquidation, dissolution or winding up on the common stock or preferred stock purchasable upon exercise, if any; or (ii) in the case of warrants for the purchase of debt securities, the right to receive payments of principal of, any premium or interest on the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture.

Outstanding Warrants

As of March 20, 2015, there were outstanding warrants to purchase 79,149,568 shares of our common stock, of which warrants to purchase 409,228 shares were outstanding with an exercise price of \$3.44 per share, warrants to purchase 1,062,500 shares were outstanding with an exercise price of \$1.00 per share, warrants to purchase 1,816,608 shares were outstanding with an exercise price of \$3.65 per share, warrants to purchase 2,046,139 shares were outstanding with an exercise price of \$2.75 per share, warrants to purchase 10,625,000 shares were outstanding with an exercise price of \$1.10 per share, warrants to purchase 28,097,400 shares were outstanding with an exercise price of \$0.65 per share, warrants to purchase 13,081,428 shares were outstanding with an exercise price of \$0.01 per share, and warrants to purchase 22,011,265 shares were outstanding with an exercise price of \$0.75 per share. The warrants may be exercised for cash or, under certain circumstances, on a cashless basis, in which case we will deliver, upon exercise, the number of shares with respect to which the warrant is being exercised reduced by a number of shares having a value (as determined in accordance with the terms of the applicable warrant) equal to the aggregate exercise

price of the shares with respect to which the warrant is being exercised.

Table of Contents

DESCRIPTION OF UNITS

The following description, together with the additional information we may include in any applicable prospectus supplement, summarizes the material terms and provisions of the units that we may offer under this prospectus. While the terms we have summarized below will apply generally to any units that we may offer under this prospectus, we will describe the particular terms of any series of units in more detail in the applicable prospectus supplement and any related free writing prospectus. The terms of any units offered under a prospectus supplement may differ from the terms described below. However, no prospectus supplement will fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from another report we file with the SEC, the form of unit agreement that describes the terms of the series of units we may offer under this prospectus, and any supplemental agreements, before the issuance of the related series of units. The following summaries of material terms and provisions of the units are subject to, and qualified in their entirety by reference to, all the provisions of the unit agreement and any supplemental agreements applicable to a particular series of units. We urge you to read the applicable prospectus supplement and any related free writing prospectus, as well as the complete unit agreement and any supplemental agreements that contain the terms of the units.

General

We may issue units comprised of one or more debt securities, shares of common stock, shares of preferred stock and warrants in any combination. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date.

We will describe in the applicable prospectus supplement the terms of the series of units, including, but not limited to:

the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;

any provisions of the governing unit agreement that differ from those described below; and

any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

The provisions described in this section, as well as those described under **Description of Common Stock and Preferred Stock**, **Description of Debt Securities** and **Description of Warrants** will apply to each unit and to any common stock, preferred stock, debt security or warrant included in each unit, respectively.

Issuance in Series

We may issue units in such amounts and in numerous distinct series as we determine.

Enforceability of Rights by Holders of Units

Each unit agent will act solely as our agent under the applicable unit agreement and will not assume any obligation or relationship of agency or trust with any holder of any unit. A single bank or trust company may act as unit agent for more than one series of units. A unit agent will have no duty or responsibility in case of any default by us under the applicable unit agreement or unit, including any duty or responsibility to initiate any

Table of Contents

proceedings at law or otherwise, or to make any demand upon us. Any holder of a unit may, without the consent of the related unit agent or the holder of any other unit, enforce by appropriate legal action its rights as holder under any security included in the unit.

We, the unit agents and any of their agents may treat the registered holder of any unit certificate as an absolute owner of the units evidenced by that certificate for any purpose and as the person entitled to exercise the rights attaching to the units so requested, despite any notice to the contrary.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee or depositary or warrant agent maintain for this purpose as the holders of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as indirect holders of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Global securities will be registered in the name of the depositary. Consequently, for global securities, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a global security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not legal holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities that are not issued in global form. In these cases, investors may choose to hold their securities in their own names or in street name. Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we or any applicable trustee or depositary will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those

securities, and we or any such trustee or depositary will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners,

Table of Contents

but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not legal holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee or third party employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the legal holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with its participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the legal holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of an indenture, or for other purposes. In such an event, we would seek approval only from the legal holders, and not the indirect holders, of the securities. Whether and how the legal holders contact the indirect holders is up to the legal holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form because the securities are represented by one or more global securities or in street name, you should check with your own institution to find out:

how it handles securities payments and notices;

whether it imposes fees or charges;

how it would handle a request for the legal holders' consent, if ever required;

whether and how you can instruct it to send you securities registered in your own name so you can be a legal holder, if that is permitted in the future;

how it would exercise rights under the securities if there were a default or other event triggering the need for legal holders to act to protect their interests; and

if the securities are in book-entry form, how the depository's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depository. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we issue to, deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depository. Unless we specify otherwise in the applicable prospectus supplement, The Depository Trust Company, New York, New York, known as DTC, will be the depository for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depository, its nominee or a successor depository, unless special termination situations arise. We describe those situations below under **Special Situations When A Global Security Will Be Terminated**. As a result of these arrangements, the depository, or its nominee, will be the sole registered owner and legal holder of all securities represented by a

Table of Contents

global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depository or with another institution that does. Thus, an investor whose security is represented by a global security will not be a legal holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued as a global security, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations For Global Securities

As an indirect holder, an investor's rights relating to a global security will be governed by the account rules of the investor's financial institution and of the depository, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depository that holds the global security.

If securities are issued only as global securities, an investor should be aware of the following:

an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;

an investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;

an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;

an investor may not be able to pledge his or her interest in the global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;

the depository's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in the global security. We and any applicable trustee have no responsibility for any aspect of the depository's actions or for its records of ownership interests in the global security. We and the trustee also do not supervise the depository in any way;

the depository may, and we understand that DTC will, require that those who purchase and sell interests in the global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and

financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in the global security, may also have their own policies affecting payments, notices and other matters relating to the securities. There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, a global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own names, so that they will be direct holders. We have described the rights of holders and street name investors above.

Table of Contents

A global security will terminate when the following special situations occur:

if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;

if we notify any applicable trustee that we wish to terminate that global security; or

if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The applicable prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the prospectus supplement. When a global security terminates, the depositary, and neither we nor any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

PLAN OF DISTRIBUTION

We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

the name or names of any agents or underwriters;

the purchase price of the securities being offered and the proceeds we will receive from the sale;

any over-allotment options under which underwriters may purchase additional securities from us;

any agency fees or underwriting discounts and other items constituting agents or underwriters compensation;

any public offering price;

any discounts or concessions allowed or reallocated or paid to dealers; and

any securities exchanges or markets on which such securities may be listed.

We may distribute the securities from time to time in one or more transactions at:

fixed price or prices, which may be changed from time to time;

market prices prevailing at the time of sale;

prices related to such prevailing market prices; or

negotiated prices.

Agents

We may designate agents who agree to use their reasonable efforts to solicit purchases of our securities for the period of their appointment or to sell our securities on a continuing basis. We will name any agent involved in the offering and sale of securities and we will describe any fees or commissions we will pay the agent in the applicable prospectus supplement.

Underwriters

If we use underwriters for a sale of securities, the underwriters will acquire the securities for their own account. The underwriters may resell the securities in one or more transactions, including negotiated transactions,

Table of Contents

at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. Subject to certain conditions, the underwriters will be obligated to purchase all the securities of the series offered if they purchase any of the securities of that series. We may change from time to time any public offering price and any discounts or concessions the underwriters allow or reallow or pay to dealers. We may use underwriters with whom we have a material relationship. We will describe the nature of any such relationship in any applicable prospectus supplement naming any such underwriter. Only underwriters we name in the prospectus supplement are underwriters of the securities offered by the prospectus supplement.

We may provide agents and underwriters with indemnification against civil liabilities related to offerings under this prospectus, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities.

Direct Sales

We may also sell securities directly to one or more purchasers without using underwriters or agents. Underwriters, dealers and agents that participate in the distribution of the securities may be underwriters as defined in the Securities Act, and any discounts or commissions they receive from us and any profit on their resale of the securities may be treated as underwriting discounts and commissions under the Securities Act. We will identify in the applicable prospectus supplement any underwriters, dealers or agents and will describe their compensation. We may have agreements with the underwriters, dealers and agents to indemnify them against specified civil liabilities, including liabilities under the Securities Act. Underwriters, dealers and agents may engage in transactions with or perform services for us in the ordinary course of their businesses.

Trading Markets and Listing of Securities

Unless otherwise specified in the applicable prospectus supplement, each class or series of securities will be a new issue with no established trading market, other than our common stock, which is currently listed on the NYSE MKT. We may elect to list any other class or series of securities on any exchange or market, but we are not obligated to do so. It is possible that one or more underwriters may make a market in a class or series of securities, but the underwriters will not be obligated to do so and may discontinue any market making at any time without notice. We cannot give any assurance as to the liquidity of the trading market for any of the securities.

Stabilization Activities

Any underwriter may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of these activities at any time.

Passive Market Making

Any underwriters who are qualified market makers on the NYSE MKT may engage in passive market making transactions in the securities on the NYSE MKT in accordance with Rule 103 of Regulation M, during the business

day prior to the pricing of the offering, before the commencement of offers or sales of the securities. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the

Table of Contents

highest independent bid for such security. If all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

LEGAL MATTERS

The validity of the securities being offered by this prospectus will be passed upon for us by DLA Piper LLP (US), San Diego, California. If the validity of any securities is also passed upon by counsel any underwriters, dealers or agents, that counsel will be named in the prospectus supplement relating to that specific offering.

EXPERTS

The consolidated financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2014 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of such firm as experts in auditing and accounting.

INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to incorporate by reference into this prospectus the information we file with the SEC. This means that we can disclose important information to you by referring you to those documents. Any statement contained in a document incorporated by reference in this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained herein, or in any subsequently filed document, which also is incorporated by reference herein, modifies or supersedes such earlier statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

We hereby incorporate by reference into this prospectus the following documents that we have filed with the SEC under the Exchange Act File No. 001-32157 (other than current reports on Form 8-K, or portions thereof, furnished under Items 2.02 or 7.01 of Form 8-K):

our Annual Report on Form 10-K for the fiscal year ended December 31, 2014, filed with the SEC on March 24, 2015;

our Current Reports on Form 8-K filed with the SEC on January 6, 2015, January 7, 2015, January 12, 2015, January 27, 2015, February 3, 2015, February 9, 2015, and March 2, 2015; and

the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on April 27, 2004 (File No. 001-32157-041020580).

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than current reports on Form 8-K, or portions thereof, furnished under Items 2.02 or 7.01 of Form 8-K) (i) after the initial filing date of the registration statement of which this prospectus forms a part and prior to the effectiveness of such registration statement and (ii) after the date of this prospectus and prior to the termination of the offering shall be deemed to be incorporated by reference in this prospectus from the date of filing of the documents, unless we specifically provide otherwise. Information that we file with the SEC will automatically update and may replace information previously filed with the SEC. To the extent that any information contained in any current report on Form

8-K or any exhibit thereto, was or is furnished to, rather than filed with the SEC, such information or exhibit is specifically not incorporated by reference.

Table of Contents

Upon written or oral request made to us at the address or telephone number below, we will, at no cost to the requester, provide to each person, including any beneficial owner, to whom this prospectus is delivered, a copy of any or all of the information that has been incorporated by reference in this prospectus (other than an exhibit to a filing, unless that exhibit is specifically incorporated by reference into that filing), but not delivered with this prospectus. You may also access this information on our website at www.masttherapeutics.com by viewing the SEC Filings subsection of the Investors menu. No additional information on our website is deemed to be part of or incorporated by reference into this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

Mast Therapeutics, Inc.

3611 Valley Centre Drive, Suite 500

San Diego, CA 92130 Attn: Investor Relations

(858) 552-0866

WHERE YOU CAN FIND MORE INFORMATION

As permitted by SEC rules, this prospectus omits certain information that is included in the registration statement of which this prospectus forms a part and its exhibits. Since this prospectus may not contain all of the information that you may find important, you should review the full text of these documents. If we have filed a contract, agreement or other document as an exhibit to the registration statement of which this prospectus forms a part, you should read the exhibit for a more complete understanding of the document or matter involved. Each statement in this prospectus, including statements incorporated by reference as discussed above, regarding a contract, agreement or other document is qualified in its entirety by reference to the actual document.

We are subject to the information reporting requirements of the Exchange Act, and, in accordance with these requirements, we file annual, quarterly and current reports, proxy statements, and other information with the SEC. You may inspect, read and copy the reports and other information we file with the SEC at the SEC's Public Reference Room located at 100 F Street, N.E., Washington, D.C. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an internet website at <http://www.sec.gov> that contains our filed reports, proxy and information statements, and other information that we file electronically with the SEC. Additionally, we make these filings available, free of charge, on our website at www.masttherapeutics.com in the SEC Filings subsection of the Investors menu as soon as reasonably practicable after we electronically file such materials with, or furnish them to, the SEC. The information on our website, other than these filings, is not, and should not be, considered part of this prospectus, is not incorporated by reference into this prospectus, and should not be relied upon in connection with making any investment decision with respect to our securities.

Table of Contents

\$150,000,000

Common Stock

Preferred Stock

Debt Securities

Warrants

Units

PROSPECTUS

, 2015

Table of Contents

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MARCH 24, 2015

PROSPECTUS

Common Stock

We have entered into a sales agreement with Cowen and Company, LLC, or Cowen, relating to shares of our common stock, \$0.001 par value per share, offered by this prospectus. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$30,000,000. As of the date of this prospectus, we had issued and sold shares of our common stock having an aggregate offering price of \$15,348,793 pursuant to the sales agreement and a prior prospectus and related prospectus supplement. Accordingly, we may offer and sell shares of our common stock having an aggregate offering price of up to \$14,651,207 pursuant to this prospectus.

Our common stock is listed on NYSE MKT under the symbol MSTX. The last reported sale price of our common stock on March 23, 2015 was \$0.52 per share.

Upon our delivery of a placement notice and subject to the terms and conditions of the sales agreement, Cowen may sell our common stock by methods deemed to be an at the market offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act, including sales made directly on the NYSE MKT, on any other existing trading market for our common stock or to or through a market maker. In addition, with our prior written approval, Cowen may also sell our common stock by any other method permitted by law, including in negotiated transactions. Cowen will act as sales agent using its commercially reasonable efforts consistent with its normal trading and sales practices and applicable state and federal laws, rules and regulations and the rules of the NYSE MKT.

We will pay Cowen a commission, or allow a discount, for its services in acting as agent in the sale of our common stock in an amount up to 3.0% of the gross sales price per share of all shares sold through it as agent under the sales agreement.

Investing in our securities involves a high degree of risk. See Risk Factors beginning on page 3 of this prospectus and in the documents incorporated by reference in this prospectus, as updated by any related free writing prospectus and other future filings we make with the Securities and Exchange Commission that are incorporated by reference into this prospectus, for a discussion of the factors you should consider carefully before deciding to purchase our securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is

truthful or complete. Any representation to the contrary is a criminal offense.

Cowen and Company

The date of this prospectus is , 2015

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	ii
<u>PROSPECTUS SUMMARY</u>	1
<u>RISK FACTORS</u>	3
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	4
<u>USE OF PROCEEDS</u>	5
<u>DILUTION</u>	5
<u>DESCRIPTION OF COMMON STOCK</u>	6
<u>PLAN OF DISTRIBUTION</u>	9
<u>LEGAL MATTERS</u>	10
<u>EXPERTS</u>	10
<u>INFORMATION INCORPORATED BY REFERENCE</u>	10
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	11

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus relates to the offering of our common stock. Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus, together with the information incorporated by reference as described under the headings **Information Incorporated by Reference** and **Where You Can Find More Information** in this prospectus. These documents contain important information that you should consider when making your investment decision.

This prospectus describes the specific terms of the common stock we are offering and also adds to, and updates information contained in the documents incorporated by reference into this prospectus. To the extent there is a conflict between the information contained in this prospectus, on the one hand, and the information contained in any document incorporated by reference into this prospectus that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus, on the other hand, you should rely on the information in this prospectus. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document filed after the date of this prospectus and incorporated by reference into this prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

You should rely only on the information contained or incorporated by reference in this prospectus and in any free writing prospectuses we may provide to you in connection with this offering. We have not, and Cowen has not, authorized any other person to provide you with any information that is different. If anyone provides you with different or inconsistent information, you should not rely on it. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus outside the United States. This prospectus does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in this prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights selected information about us, this offering and information appearing elsewhere in this prospectus and in the documents we incorporate by reference. This summary is not complete and does not contain all the information you should consider before investing in our common stock pursuant to this prospectus. Before making an investment decision, to fully understand this offering and its consequences to you, you should carefully read this entire prospectus, including Risk Factors beginning on page 3 of this prospectus and the financial statements and related notes and the other information that we incorporated by reference herein, including our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q that we file from time to time.

Unless the context otherwise requires, all references in this prospectus to Mast, we, us, our, the Company or similar words refer to Mast Therapeutics, Inc., together with our consolidated subsidiaries.

Company Overview

We are a clinical-stage, biopharmaceutical company developing novel therapies for serious or life-threatening diseases with significant unmet needs. We are leveraging our Molecular Adhesion & Sealant Technology, or MAST, platform, derived from over two decades of clinical, nonclinical, and manufacturing experience with purified and non-purified poloxamers, to develop MST-188 (vepoloxamer) Injection, our lead product candidate. Vepoloxamer has demonstrated multiple pharmacologic effects that may provide clinical benefit in a wide range of diseases and conditions typically characterized by impaired microvascular blood flow and/or damaged cell membranes. We currently are developing vepoloxamer for the treatment of sickle cell disease, arterial disease (in combination with thrombolytics), and heart failure. We also are developing AIR001, a sodium nitrite solution for intermittent inhalation via nebulizer. AIR001 has demonstrated positive hemodynamic effects in patients with pulmonary hypertension and we are developing it for the treatment of heart failure with preserved ejection fraction, or HFpEF.

We have devoted substantially all of our resources to research and development and to acquisition of our product candidates. We have not yet marketed or sold any products or generated any significant revenue and we have incurred significant annual operating losses since inception. We incurred losses from operations of \$29.3 million and \$21.5 million for the years ended December 31, 2014 and December 31, 2013, respectively. As of December 31, 2014, we had an accumulated deficit of \$235.1 million. Our cash, cash equivalents, and investment securities were \$57.3 million as of December 31, 2014.

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

Our second product candidate, AIR001, is being tested in multiple institution-sponsored Phase 2a clinical studies in patients with HFpEF. We obtained the AIR001 program through our acquisition of Aires Pharmaceuticals, Inc. in February 2014. Prior to the acquisition, AIR001 had been tested in more than 120 healthy volunteers and patients with various forms of pulmonary hypertension and it demonstrated positive hemodynamic effects and was well-tolerated. If data from the Phase 2a studies are positive, we expect to conduct a Phase 2b proof-of-concept study in HFpEF.

Table of Contents

Corporate Information

In March 2013, we changed our name from ADVENTRX Pharmaceuticals, Inc. to Mast Therapeutics, Inc.

Our principal executive offices are located at 3611 Valley Centre Drive, Suite 500, San Diego, CA 92130 and our telephone number at that address is (858) 552-0866. Our corporate website is located at www.masttherapeutics.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and 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, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The information contained in, or that can be accessed through, our website is not part of this prospectus.

The Offering

Common stock offered by us: Shares having an aggregate offering price up to \$14,651,207.

Manner of offering: At the market offering that may be made from time to time through our agent, Cowen and Company, LLC. See Plan of Distribution on page 9.

Use of proceeds: We plan to use the net proceeds from this offering for working capital and general corporate purposes, which include, but are not limited to, funding clinical development of and seeking regulatory approval for our product candidates. Please see Use of Proceeds on page 5.

Risk factors: See Risk Factors beginning on page 3 of this prospectus, as well as the other information included in or incorporated by reference in this prospectus, for a discussion of risks you should carefully consider before investing in our common stock.

NYSE MKT symbol: MSTX.

Table of Contents

RISK FACTORS

Investing in our common stock involves a high degree of risk and uncertainty. In addition to the other information included or incorporated by reference in this prospectus, you should carefully consider the risks described in the Risk Factors section of our Form 10-K for the year ended December 31, 2014, which is incorporated by reference herein, before making an investment decision with respect to our common stock. We expect to update these Risk Factors from time to time in the periodic and current reports that we file with the SEC after the date of this prospectus. These updated Risk Factors will be incorporated by reference in this prospectus. Please refer to these subsequent reports for additional information relating to the risks associated with investing in our common stock. If any of such risks and uncertainties actually occurs, our business, financial condition, and results of operations could be severely harmed. This could cause the trading price of our common stock to decline, and you could lose all or part of your investment.

Risks Related to this Offering

Resales of our common stock in the public market during this offering by our stockholders may cause the market price of our common stock to fall.

We may issue common stock from time to time in connection with this offering. The issuance from time to time of these new shares of our common stock, or our ability to issue new shares of common stock in this offering, could result in resales of our common stock by our current stockholders concerned about the potential dilution of their holdings. In turn, these resales could have the effect of depressing the market price for our common stock.

There may be future sales or other dilution of our equity, which may adversely affect the market price of our common stock.

We are generally not restricted from issuing additional common stock, including any securities that are convertible into or exchangeable for, or that represent the right to receive, common stock. The market price of our common stock could decline as a result of sales of common stock or securities that are convertible into or exchangeable for, or that represent the right to receive, common stock after this offering or the perception that such sales could occur.

Our management will have broad discretion over the use of the net proceeds from this offering, you may not agree with how we use the proceeds and the proceeds may not be invested successfully.

We have not designated any portion of the net proceeds from this offering to be used for any particular purpose. Accordingly, our management will have broad discretion as to the use of the net proceeds from this offering and could use them for purposes other than those contemplated at the time of commencement of this offering. Accordingly, you will be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that, pending their use, we may invest the net proceeds in a way that does not yield a favorable, or any, return for our company.

You may experience immediate and substantial dilution in the book value per share of the common stock you purchase.

Because the prices per share at which shares of our common stock are sold in this offering may be substantially higher than the book value per share of our common stock, you may suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering. The shares sold in this offering, if any, will be

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

sold from time to time at various prices. After giving effect to the sale of our common stock in the maximum aggregate offering amount of \$14,651,207 at an assumed offering price of \$0.49

Table of Contents

per share, the last reported sale price of our common stock on the NYSE MKT on March 20, 2015 and after deducting estimated offering commissions and expenses payable by us, our net tangible book value as of December 31, 2014 would have been \$61.3 million, or \$0.33 per share of common stock. This represents an immediate increase in the net tangible book value of \$0.03 per share to our existing stockholders and an immediate and substantial dilution in as-adjusted net tangible book value of \$0.16 per share to new investors who purchase our common stock in the offering. See Dilution for a more detailed discussion of the dilution you may incur in connection with this offering.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and our SEC filings that are incorporated by reference into this prospectus contain or incorporate by reference forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. All statements, other than statements of historical fact, included or incorporated by reference in this prospectus regarding our development of our products, financial position, strategy, regulatory status, clinical and nonclinical studies, collaborations, commercial prospects, internal growth, competition, intellectual property, regulatory reforms, products, objectives of management, and compliance with NYSE MKT listing standards are forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

the initiation, scope, rate of progress, results and timing of our clinical and nonclinical studies of our product candidates, including vepoloxamer;

the successful completion of our development programs and our ability to manage costs associated with clinical and nonclinical development of our product candidates, including vepoloxamer;

our ability to obtain and maintain regulatory approvals of our product candidates, including vepoloxamer;

our ability to commercialize and achieve market acceptance of our product candidates, including vepoloxamer;

our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others;

our estimates regarding the sufficiency of our cash resources and our need for additional funding; and

our intended use of the net proceeds from offerings of our securities under this prospectus.

The words believe, anticipate, estimate, plan, expect, intend, may, could, should, potential, will, and would and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements reflect our current views with respect to future events, are based on assumptions and are subject to risks and uncertainties. We cannot guarantee that we actually will achieve the plans, intentions or expectations expressed in our forward-looking statements and you should not place undue reliance on these statements. There are a number of important factors that could cause our

actual results to differ materially from those indicated or implied by forward-looking statements. These important factors include those discussed under the heading "Risk Factors" contained or incorporated in this prospectus and in the applicable prospectus supplement and any free writing prospectus we may authorize for use in connection with a specific offering. These factors and the other cautionary statements made in this prospectus should be read as being applicable to all related forward-looking statements whenever they appear in this prospectus. Except as required by law, we do not assume any obligation to update any forward-looking statement. We disclaim any intention or obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

Table of Contents**USE OF PROCEEDS**

We will have broad discretion in the use of the net proceeds from any sale of securities offered under this prospectus. We intend to use the net proceeds for working capital and general corporate purposes, which include, but are not limited to, the funding of clinical development of and pursuing regulatory approval for our product candidates, general and administrative expenses, and the acquisition of companies, businesses or assets.

We have not determined the amount of net proceeds to be used specifically for such purposes. Pending the use of any net proceeds, we expect to invest the net proceeds in interest-bearing, marketable securities.

DILUTION

If you invest in our common stock, your interest will be diluted to the extent of the difference between the public offering price per share and the net tangible book value per share of our common stock after this offering immediately after giving effect to this offering.

The net tangible book value of our common stock as of December 31, 2014, was approximately \$47.1 million, or approximately \$0.30 per share. Net tangible book value per share represents the amount of our total tangible assets less the amount of our total tangible liabilities, divided by the total number of shares of our common stock outstanding. Dilution per share to new investors represents the difference between the amount per share paid by purchasers for each share of common stock in this offering and the net tangible book value per share of our common stock immediately following the completion of this offering.

After giving effect to the sale of shares of our common stock in the aggregate amount of \$14,651,207 at an assumed offering price of \$0.49 per share, which was the last reported sale price of our common stock on March 20, 2015 on the NYSE MKT, and after deducting estimated commissions and estimated offering expenses, our as-adjusted net tangible book value as of December 31, 2014 would have been approximately \$61.3 million, or approximately \$0.33 per share. This represents an immediate increase in net tangible book value of approximately \$0.03 per share to our existing stockholders and an immediate dilution in as-adjusted net tangible book value of approximately \$0.16 per share to purchasers of our common stock in this offering, as illustrated by the following table:

Assumed offering price per share		\$ 0.49
Net tangible book value per share as of December 31, 2014	\$ 0.30	
Increase per share attributable to this offering	\$ 0.03	
As-adjusted net tangible book value per share as of December 31, 2014, after giving effect to this offering		\$ 0.33
Dilution per share to new investors participating in this offering		\$ 0.16

The table above assumes, for illustrative purposes only, an aggregate of 29,900,422 shares of our common stock are sold at a price of \$0.49 per share, for aggregate gross proceeds of \$14,651,207. The shares, if any, sold in this offering will be sold from time to time at various prices. An increase of \$0.10 per share in the price at which the shares are sold from the assumed offering price of \$0.49 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$14,651,207 is sold at that price, would increase the adjusted net tangible book value per share after the offering to \$0.34 per share and increase the dilution in net tangible book value per share to new investors in this offering to \$0.25 per share, after deducting commissions and estimated aggregate offering expenses payable by

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

us. A decrease of \$0.10 per share in the price at which the shares are sold from the assumed offering price of \$0.49 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$14,651,207 is sold at that price, would decrease the adjusted net tangible book value per share after the offering to \$0.31 per share and decrease the dilution in net tangible book value per share to new investors in this offering to \$0.08 per share, after deducting commissions and estimated aggregate offering expenses payable by us. This information is supplied for illustrative purposes only.

Table of Contents

The table above is based on 159,458,376 shares of our common stock outstanding as of December 31, 2014 and excludes:

13,081,428 shares of our common stock issuable upon exercise of pre-funded warrants outstanding as of December 31, 2014, with an exercise price of \$0.01 per share;

66,068,140 shares of our common stock issuable upon exercise of warrants outstanding as of December 31, 2014, with a weighted-average exercise price of \$0.93 per share;

13,616,137 shares of our common stock issuable upon exercise of options outstanding as of December 31, 2014, with a weighted-average exercise price of \$1.00 per share;

10,388,691 shares and 306,945 shares of our common stock available for future grants under our 2014 Omnibus Incentive Plan and 2005 Employee Stock Purchase Plan as of December 31, 2014, respectively; and

12,478,050 shares of common stock that may be issued to the former stockholders of SynthRx, Inc., subject to the achievement of performance milestones, pursuant to the terms of the merger agreement with SynthRx. To the extent that any outstanding options or warrants are exercised, new options are issued under our equity incentive plan, shares of common stock are sold under our employee stock purchase plan or we otherwise issue additional shares of common stock in the future at prices per share below the price per share for any shares sold in this offering, there will be further dilution to new investors.

DESCRIPTION OF COMMON STOCK

The following description of our common stock, together with any additional information we include in any free writing prospectus, summarizes the material terms and provisions of our common stock offered under this prospectus. For the complete terms of our common stock, please refer to our certificate of incorporation and our bylaws, as amended to date, that are incorporated by reference into the registration statement of which this prospectus is a part or may be incorporated by reference in this prospectus. The terms of our common stock may also be affected by the Delaware General Corporation Law, or the DGCL. The summary below and that contained in any free writing prospectus are qualified in their entirety by reference to our certificate of incorporation and bylaws, as in effect at the time of any offering of securities under this prospectus.

Common Stock

As of the date of this prospectus, our certificate of incorporation authorizes us to issue 500,000,000 shares of common stock, par value \$0.001 per share, of which 159,458,376 shares were issued and outstanding as of March 20, 2015. Additional shares of authorized common stock may be issued, as authorized by our board of directors from time to time, without stockholder approval, except as may be required by applicable securities exchange requirements. The holders of common stock possess exclusive voting rights in us, except to the extent our board of directors specifies voting power with respect to any other class of securities issued in the future. Each holder of our common stock is

entitled to one vote for each share held of record on each matter submitted to a vote of stockholders, including the election of directors. Stockholders do not have any right to cumulate votes in the election of directors.

Subject to preferences that may be granted to the holders of preferred stock, each holder of our common stock is entitled to share ratably in distributions to stockholders and to receive ratably such dividends as may be declared by our board of directors out of funds legally available therefor. In the event of our liquidation, dissolution or winding up, the holders of our common stock will be entitled to receive, after payment of all of our debts and liabilities and of all sums to which holders of any preferred stock may be entitled, the distribution of any of our remaining assets. Holders of our common stock have no conversion, exchange, sinking fund or redemption rights and have no preemptive rights to subscribe for any of our securities.

Table of Contents

All of the outstanding shares of our common stock are fully paid and non-assessable. The shares of common stock offered by this prospectus, when issued and paid for, will also be, fully paid and non-assessable.

Securities Exchange Listing

Our common stock is listed on the NYSE MKT under the symbol MSTX.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company.

Anti-Takeover Effects of Provisions of our Charter Documents and Delaware Law

Provisions of the DGCL, our certificate of incorporation and our bylaws could make it more difficult to acquire us by means of a tender offer, a proxy contest or otherwise, or to remove incumbent officers and directors. These provisions, summarized below, are expected to discourage certain types of coercive takeover practices and takeover bids that our board of directors may consider inadequate and to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of increased protection of our ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging takeover or acquisition proposals because, among other things, negotiation of these proposals could result in an improvement of their terms. This summary does not purport to be complete and is qualified in its entirety by reference to the DGCL and our certificate of incorporation and bylaws.

Certificate of Incorporation and Bylaws

Preferred Stock. Under our certificate of incorporation, our board of directors has the power to authorize the issuance of up to 1,000,000 shares of preferred stock, all of which are currently undesignated, and to determine the price, rights, preferences, privileges and restrictions, including voting rights, of those shares without further vote or action by our stockholders. The issuance of preferred stock may:

delay, defer or prevent a change in control;

discourage bids for our common stock at a premium over the market price of our common stock;

adversely affect the voting and other rights of the holders of our common stock; and

discourage acquisition proposals or tender offers for our shares and, as a consequence, inhibit fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Advance Notice Requirement. Stockholder nominations of individuals for election to our board of directors and stockholder proposals of other matters to be brought before an annual meeting of our stockholders must comply with the advance notice procedures set forth in our bylaws. Generally, to be timely, such notice must be received at our principal executive offices no later than the date specified in our proxy statement released to stockholders in connection with the preceding year's annual meeting of stockholders, which date shall be not earlier than the 120th

day, nor later than the close of business on the 90th day, prior to the first anniversary of the date of the preceding year's annual meeting of stockholders.

Special Meeting Requirements. Our bylaws provide that special meetings of our stockholders may be called only at the request of our board of directors, president (unless there is a chief executive officer who is not the president, in which case a special meeting may be called at any time by the chief executive officer and not the president) or chair of the board of directors. Only such business shall be considered at a special meeting as shall have been stated in the notice for such meeting.

Table of Contents

No Cumulative Voting. Our certificate of incorporation does not include a provision for cumulative voting for directors.

Indemnification. Our certificate of incorporation and bylaws provide that we will indemnify our officers and directors against losses as they incur in investigations and legal proceedings resulting from their services to us, which may include service in connection with takeover defense measures.

Removal of Directors. Our bylaws provide that the affirmative vote of the holders of at least 75% of our voting stock then outstanding is required to remove our directors, either with or without cause.

Authorized but Unissued Shares. Our authorized but unissued shares of common stock and preferred stock will be available for future issuance without stockholder approval. We may use additional shares for a variety of purposes, including future public offerings to raise additional capital, to fund acquisitions and as employee compensation. The existence of authorized but unissued shares of common stock and preferred stock could render more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the DGCL, an anti-takeover law. In general, Section 203 prohibits, with some exceptions, a publicly held Delaware corporation from engaging in a business combination with any interested stockholder for a period of three years following the date that stockholder became an interested stockholder, unless:

prior to that date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares of voting stock outstanding (but not the voting stock owned by the interested stockholder) those shares owned by persons who are directors and officers and by excluding employee stock plans in which employee participants do not have the right to determine whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to that date, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66-2/3% of the outstanding voting stock that is not owned by the interested stockholder.

Section 203 defines business combination to include any of the following:

any merger or consolidation involving the corporation and the interested stockholder;

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

Table of Contents

In general, Section 203 defines an interested stockholder as any person who, together with the person's affiliates and associates, beneficially owns, or within three years prior to the determination of interested stockholder status did beneficially own, 15% or more of the outstanding voting stock of the corporation.

The above provisions may deter a hostile takeover or delay a change in control of management or us.

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Cowen and Company, LLC, or Cowen, under which we may issue and sell from time to time shares of our common stock having an aggregate offering price of up to \$30,000,000 through Cowen as our sales agent. As of the date of this prospectus, we had issued and sold shares of our common stock having an aggregate offering price of \$15,348,793 pursuant to the sales agreement and a prior prospectus and related prospectus supplement. Accordingly, we may offer and sell shares of our common stock having an aggregate offering price of up to \$14,651,207 pursuant to this prospectus.

Sales of the common stock, if any, will be made at market prices by any method permitted by law deemed to be an at the market offering as defined in Rule 415 under the Securities Act, including sales made through the NYSE MKT and any other existing trading market for the common stock, or to or through a market maker. In addition, with our express authorization, Cowen may also sell our common stock in negotiated transactions.

Cowen will offer the common stock subject to the terms and conditions of the sales agreement on a daily basis or as otherwise agreed upon by us and Cowen. We will designate the maximum amount of common stock to be sold through Cowen on a daily basis or otherwise determine such maximum amount together with Cowen. Subject to the terms and conditions of the sales agreement, Cowen will use its commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us. We may instruct Cowen not to sell common stock if the sales cannot be effected at or above the price designated by us in any such instruction. We or Cowen may suspend the offering of the common stock being made through Cowen under the sales agreement upon proper notice to the other party. We and Cowen each have the right, by giving written notice as specified in the sales agreement, to terminate the sales agreement in each party's sole discretion at any time.

The aggregate compensation payable to Cowen as sales agent will be up to 3.0% of the gross proceeds from the sales of our common stock pursuant to the sales agreement.

The remaining sales proceeds, after deducting any expenses payable by us and any transaction fees imposed by any governmental, regulatory, or self-regulatory organization in connection with the sales, will equal our net proceeds for the sale of such common stock.

Cowen will provide written confirmation to us following the close of trading on the NYSE MKT as applicable, each day in which common stock is sold through it as sales agent under the sales agreement. Each confirmation will include the number of shares of common stock sold through it as sales agent on that day, the gross sales price per share, the net proceeds to us and the compensation payable by us to Cowen.

We will report at least quarterly the number of shares of common stock sold through Cowen under the sales agreement, the net proceeds to us and the compensation paid by us to Cowen in connection with the sales of common stock.

Settlement for sales of common stock will occur, unless the parties agree otherwise, on the third business day that is also a trading day following the date on which any sales were made in return for payment of the net proceeds to us.

There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

Table of Contents

In connection with the sales of the common stock on our behalf, Cowen may be deemed to be an underwriter within the meaning of the Securities Act, and the compensation paid to Cowen may be deemed to be underwriting commissions or discounts. We have agreed in the sales agreement to provide indemnification and contribution to Cowen against certain liabilities, including liabilities under the Securities Act. In addition, we have agreed, under certain circumstances, to reimburse a portion of the expenses of Cowen incurred in connection with this offering up to a maximum of \$30,000. As sales agent, Cowen will not engage in any transactions that stabilize our common stock.

We estimate that the total expenses of the offering payable by us, excluding commissions payable to Cowen under the sales agreement, will be approximately \$120,000.

This summary of the material provisions of the sales agreement does not purport to be a complete statement of its terms and conditions. Copies of the sales agreement that we entered into with Cowen are filed with the SEC and are incorporated by reference into the registration statement of which this prospectus is a part. See [Where You Can Find More Information](#) below.

LEGAL MATTERS

DLA Piper LLP (US), San Diego, California, has passed upon the validity of the common stock offered by this prospectus. Cowen and Company, LLC is being represented in connection with this offering by LeClairRyan, A Professional Corporation, New York, New York.

EXPERTS

The consolidated financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2014 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of such firm as experts in auditing and accounting.

INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to incorporate by reference into this prospectus the information we file with the SEC. This means that we can disclose important information to you by referring you to those documents. Any statement contained in a document incorporated by reference in this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained herein, or in any subsequently filed document, which also is incorporated by reference herein, modifies or supersedes such earlier statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

We hereby incorporate by reference into this prospectus the following documents that we have filed with the SEC under the Exchange Act File No. 001-32157 (other than current reports on Form 8-K, or portions thereof, furnished under Items 2.02 or 7.01 of Form 8-K):

our Annual Report on Form 10-K for the fiscal year ended December 31, 2014, filed with the SEC on March 24, 2015;

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

our Current Reports on Form 8-K filed with the SEC on January 6, 2015, January 7, 2015, January 12, 2015, January 27, 2015, February 3, 2015, February 9, 2015, and March 2, 2015; and

Table of Contents

the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on April 27, 2004 (File No. 001-32157-041020580).

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than current reports on Form 8-K, or portions thereof, furnished under Items 2.02 or 7.01 of Form 8-K) (i) after the initial filing date of the registration statement of which this prospectus forms a part and prior to the effectiveness of such registration statement and (ii) after the date of this prospectus and prior to the termination of the offering shall be deemed to be incorporated by reference in this prospectus from the date of filing of the documents, unless we specifically provide otherwise. Information that we file with the SEC will automatically update and may replace information previously filed with the SEC. To the extent that any information contained in any current report on Form 8-K or any exhibit thereto, was or is furnished to, rather than filed with the SEC, such information or exhibit is specifically not incorporated by reference.

Upon written or oral request made to us at the address or telephone number below, we will, at no cost to the requester, provide to each person, including any beneficial owner, to whom this prospectus is delivered, a copy of any or all of the information that has been incorporated by reference in this prospectus (other than an exhibit to a filing, unless that exhibit is specifically incorporated by reference into that filing), but not delivered with this prospectus. You may also access this information on our website at www.masttherapeutics.com by viewing the SEC Filings subsection of the Investors menu. No additional information on our website is deemed to be part of or incorporated by reference into this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

Mast Therapeutics, Inc.

3611 Valley Centre Drive, Suite 500

San Diego, CA 92130

Attn: Investor Relations

(858) 552-0866

WHERE YOU CAN FIND MORE INFORMATION

As permitted by SEC rules, this prospectus omits certain information that is included in the registration statement of which this prospectus forms a part and its exhibits. Since this prospectus may not contain all of the information that you may find important, you should review the full text of these documents. If we have filed a contract, agreement or other document as an exhibit to the registration statement of which this prospectus forms a part, you should read the exhibit for a more complete understanding of the document or matter involved. Each statement in this prospectus, including statements incorporated by reference as discussed above, regarding a contract, agreement or other document is qualified in its entirety by reference to the actual document.

We are subject to the information reporting requirements of the Exchange Act, and, in accordance with these requirements, we file annual, quarterly and current reports, proxy statements, and other information with the SEC. You may inspect, read and copy the reports and other information we file with the SEC at the SEC's Public Reference Room located at 100 F Street, N.E., Washington, D.C. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an internet website at <http://www.sec.gov> that contains our filed reports, proxy and information statements, and other information that we file electronically with the SEC. Additionally, we make these filings available, free of charge, on our website at www.masttherapeutics.com in the SEC Filings subsection of the Investors menu as soon as reasonably practicable.

after we electronically file such materials with, or furnish them to, the SEC. The information on our website, other than these filings, is not, and should not be, considered part of this prospectus, is not incorporated by reference into this prospectus, and should not be relied upon in connection with making any investment decision with respect to our securities.

Table of Contents

Common Stock

PROSPECTUS

Cowen and Company

, 2015

Table of Contents

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MARCH 24, 2015

PROSPECTUS

13,081,428 Shares of Common Stock Underlying Pre-Funded Warrants

22,011,265 Shares of Common Stock Underlying Warrants

This prospectus relates to the offer and sale by us of up to 35,092,693 shares of our common stock that are issuable upon the exercise of outstanding warrants. The warrants were originally issued by us on November 12, 2014, pursuant to a prospectus dated May 1, 2012, and a related prospectus supplement dated November 6, 2014. Warrants to purchase 13,081,428 shares of our common stock have an exercise price of \$0.01 per share and are referred to as the pre-funded warrants, and warrants to purchase 22,011,265 shares of our common stock have an exercise price of \$0.75 per share. We will receive the proceeds from any cash exercises of the pre-funded warrants and the warrants. Each of the pre-funded warrants and warrants is exercisable at any time until it expires on November 12, 2019.

Our common stock is listed on NYSE MKT under the symbol MSTX. The last reported sale price of our common stock on March 23, 2015 was \$0.52 per share. Neither the pre-funded warrants nor the warrants are listed, and we do not intend to apply to list them, on the NYSE MKT or any other national securities exchange.

Investing in our securities involves a high degree of risk. See Risk Factors beginning on page 3 of this prospectus and in the documents incorporated by reference in this prospectus, as updated by any related free writing prospectus and other future filings we make with the Securities and Exchange Commission that are incorporated by reference into this prospectus, for a discussion of the factors you should consider carefully before deciding to purchase our securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is _____, 2015

Table of Contents

TABLE OF CONTENTS

<u>ABOUT THIS PROSPECTUS</u>	ii
<u>PROSPECTUS SUMMARY</u>	1
<u>RISK FACTORS</u>	3
<u>SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS</u>	4
<u>USE OF PROCEEDS</u>	5
<u>DILUTION</u>	5
<u>DESCRIPTION OF COMMON STOCK</u>	6
<u>PLAN OF DISTRIBUTION</u>	9
<u>LEGAL MATTERS</u>	9
<u>EXPERTS</u>	9
<u>INFORMATION INCORPORATED BY REFERENCE</u>	9
<u>WHERE YOU CAN FIND MORE INFORMATION</u>	10

Table of Contents

ABOUT THIS PROSPECTUS

This prospectus relates to the offering of our common stock issuable upon the exercise of outstanding pre-funded warrants and warrants that were originally issued on November 12, 2014. Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus, together with the information incorporated by reference as described under the headings **Information Incorporated by Reference** and **Where You Can Find More Information** in this prospectus. These documents contain important information that you should consider when making your investment decision.

This prospectus describes the specific terms of the common stock issuable upon exercise of the above-referenced outstanding warrants and also adds to, and updates information contained in the documents incorporated by reference into this prospectus. To the extent there is a conflict between the information contained in this prospectus, on the one hand, and the information contained in any document incorporated by reference into this prospectus that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus, on the other hand, you should rely on the information in this prospectus. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document filed after the date of this prospectus and incorporated by reference into this prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

You should rely only on the information contained or incorporated by reference in this prospectus and in any free writing prospectuses we may provide to you in connection with this offering. We have not authorized any other person to provide you with any information that is different. If anyone provides you with different or inconsistent information, you should not rely on it. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus outside the United States. This prospectus does not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in this prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights selected information about us, this offering and information appearing elsewhere in this prospectus and in the documents we incorporate by reference. This summary is not complete and does not contain all the information you should consider before investing in our common stock pursuant to this prospectus. Before making an investment decision, to fully understand this offering and its consequences to you, you should carefully read this entire prospectus, including Risk Factors beginning on page 3 of this prospectus and the financial statements and related notes and the other information that we incorporated by reference herein, including our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q that we file from time to time.

Unless the context otherwise requires, all references in this prospectus to Mast, we, us, our, the Company or similar words refer to Mast Therapeutics, Inc., together with our consolidated subsidiaries.

Company Overview

We are a clinical-stage, biopharmaceutical company developing novel therapies for serious or life-threatening diseases with significant unmet needs. We are leveraging our Molecular Adhesion & Sealant Technology, or MAST, platform, derived from over two decades of clinical, nonclinical, and manufacturing experience with purified and non-purified poloxamers, to develop MST-188 (vepoloxamer) Injection, our lead product candidate. Vepoloxamer has demonstrated multiple pharmacologic effects that may provide clinical benefit in a wide range of diseases and conditions typically characterized by impaired microvascular blood flow and/or damaged cell membranes. We currently are developing vepoloxamer for the treatment of sickle cell disease, arterial disease (in combination with thrombolytics), and heart failure. We also are developing AIR001, a sodium nitrite solution for intermittent inhalation via nebulizer. AIR001 has demonstrated positive hemodynamic effects in patients with pulmonary hypertension and we are developing it for the treatment of heart failure with preserved ejection fraction, or HFpEF.

We have devoted substantially all of our resources to research and development and to acquisition of our product candidates. We have not yet marketed or sold any products or generated any significant revenue and we have incurred significant annual operating losses since inception. We incurred losses from operations of \$29.3 million and \$21.5 million for the years ended December 31, 2014 and December 31, 2013, respectively. As of December 31, 2014, we had an accumulated deficit of \$235.1 million. Our cash, cash equivalents, and investment securities were \$57.3 million as of December 31, 2014.

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

Our second product candidate, AIR001, is being tested in multiple institution-sponsored Phase 2a clinical studies in patients with HFpEF. We obtained the AIR001 program through our acquisition of Aires Pharmaceuticals, Inc. in February 2014. Prior to the acquisition, AIR001 had been tested in more than 120 healthy volunteers and patients with various forms of pulmonary hypertension and it demonstrated positive hemodynamic effects and was well-tolerated. If data from the Phase 2a studies are positive, we expect to conduct a Phase 2b proof-of-concept study in HFpEF.

Table of Contents

Corporate Information

In March 2013, we changed our name from ADVENTRX Pharmaceuticals, Inc. to Mast Therapeutics, Inc.

Our principal executive offices are located at 3611 Valley Centre Drive, Suite 500, San Diego, CA 92130 and our telephone number at that address is (858) 552-0866. Our corporate website is located at www.masttherapeutics.com. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and 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, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The information contained in, or that can be accessed through, our website is not part of this prospectus.

The Offering

Securities offered	This offering involves the offer and sale by us of up to 35,092,693 shares of our common stock that are issuable upon the exercise of outstanding pre-funded warrants and warrants. The pre-funded warrants and warrants were originally issued by us on November 12, 2014. Pre-funded warrants to purchase up to 13,081,428 shares of our common stock have an exercise price of \$0.01 per share, and warrants to purchase up to 22,011,265 shares of our common stock have an exercise price of \$0.75 per share. Each warrant is exercisable at any time until it expires on November 12, 2019. Upon exercise of the pre-funded warrants and warrants for cash, the holders of the pre-funded warrants and warrants would pay us the applicable exercise price per share of common stock. If the pre-funded warrants and warrants are exercised in full for cash, we will receive an aggregate of approximately \$16.6 million.
Use of proceeds	We plan to use the net proceeds from this offering for working capital and general corporate purposes, which include, but are not limited to, funding clinical development of and seeking regulatory approval for our product candidates. Please see Use of Proceeds on page 5.
Risk factors	See Risk Factors beginning on page 3 of this prospectus, as well as the other information included in or incorporated by reference in this prospectus, for a discussion of risks you should carefully consider before investing in our common stock.
NYSE MKT symbol	Our common stock is listed on the NYSE MKT under the symbol MSTX .
Transfer agent, warrant agent and registrar	American Stock Transfer & Trust Company, LLC

Table of Contents

RISK FACTORS

Investing in our common stock involves a high degree of risk and uncertainty. In addition to the other information included or incorporated by reference in this prospectus, you should carefully consider the risks described in the Risk Factors section of our Form 10-K for the year ended December 31, 2014, which is incorporated by reference herein, before making an investment decision with respect to our common stock. We expect to update these Risk Factors from time to time in the periodic and current reports that we file with the SEC after the date of this prospectus. These updated Risk Factors will be incorporated by reference in this prospectus. Please refer to these subsequent reports for additional information relating to the risks associated with investing in our common stock. If any of such risks and uncertainties actually occurs, our business, financial condition, and results of operations could be severely harmed. This could cause the trading price of our common stock to decline, and you could lose all or part of your investment.

Risks Related to this Offering

Resales of our common stock in the public market during this offering by our stockholders may cause the market price of our common stock to fall.

We may issue common stock from time to time in connection with this offering. The issuance from time to time of these new shares of our common stock, or our ability to issue new shares of common stock in this offering, could result in resales of our common stock by our current stockholders concerned about the potential dilution of their holdings. In turn, these resales could have the effect of depressing the market price for our common stock.

There may be future sales or other dilution of our equity, which may adversely affect the market price of our common stock.

We are generally not restricted from issuing additional common stock, including any securities that are convertible into or exchangeable for, or that represent the right to receive, common stock. The market price of our common stock could decline as a result of sales of common stock or securities that are convertible into or exchangeable for, or that represent the right to receive, common stock after this offering or the perception that such sales could occur.

Our management will have broad discretion over the use of the net proceeds from this offering, you may not agree with how we use the proceeds and the proceeds may not be invested successfully.

We have not designated any portion of the net proceeds from this offering to be used for any particular purpose. Accordingly, our management will have broad discretion as to the use of the net proceeds from this offering and could use them for purposes other than those contemplated at the time of commencement of this offering. Accordingly, you will be relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used appropriately. It is possible that, pending their use, we may invest the net proceeds in a way that does not yield a favorable, or any, return for our company.

Holders of the pre-funded warrants and warrants will experience immediate and substantial dilution in the book value per share of the common stock you purchase.

This offering involves the offer and sale by us of up to 35,092,693 shares of our common stock that are issuable upon the exercise of outstanding pre-funded warrants and warrants. The pre-funded warrants are exercisable for up to 13,081,428 shares of our common stock at an exercise price of \$0.01 per share, and the warrants are exercisable for up

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

to 22,011,265 shares of our common stock at an exercise price of \$0.75 per share. The exercise price of the warrants (\$0.75 per share) may be substantially higher than the book value per share of

Table of Contents

our common stock, and you may suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering upon exercise of such warrants. Assuming that all 35,092,693 shares of our common stock are sold in this offering upon the exercise of the pre-funded warrants and warrants for cash, those who exercise the warrants will experience immediate dilution of \$0.38 per share, representing the difference between our as adjusted net tangible book value per share as of December 31, 2014 after giving effect to this offering. The exercise of outstanding stock options and warrants may result in further dilution of your investment. See Dilution for a more detailed discussion of the dilution you may incur in connection with this offering.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and our SEC filings that are incorporated by reference into this prospectus contain or incorporate by reference forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. All statements, other than statements of historical fact, included or incorporated by reference in this prospectus regarding our development of our products, financial position, strategy, regulatory status, clinical and nonclinical studies, collaborations, commercial prospects, internal growth, competition, intellectual property, regulatory reforms, products, objectives of management, and compliance with NYSE MKT listing standards are forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

the initiation, scope, rate of progress, results and timing of our clinical and nonclinical studies of our product candidates, including vepoloxamer;

the successful completion of our development programs and our ability to manage costs associated with clinical and nonclinical development of our product candidates, including vepoloxamer;

our ability to obtain and maintain regulatory approvals of our product candidates, including vepoloxamer;

our ability to commercialize and achieve market acceptance of our product candidates, including vepoloxamer;

our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others;

our estimates regarding the sufficiency of our cash resources and our need for additional funding; and

our intended use of the net proceeds from offerings of our securities under this prospectus.

The words believe, anticipate, estimate, plan, expect, intend, may, could, should, potential, like, will, and would and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements reflect our current views with respect to future events, are based on assumptions and are subject to risks and uncertainties. We cannot guarantee that we actually will achieve the plans, intentions or expectations expressed in our forward-looking statements and

you should not place undue reliance on these statements. There are a number of important factors that could cause our actual results to differ materially from those indicated or implied by forward-looking statements. These important factors include those discussed under the heading **Risk Factors** contained or incorporated in this prospectus and in the applicable prospectus supplement and any free writing prospectus we may authorize for use in connection with a specific offering. These factors and the other cautionary statements made in this prospectus should be read as being applicable to all related forward-looking statements whenever they appear in this prospectus. Except as required by law, we do not assume any obligation to update any forward-looking statement. We disclaim any intention or obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

Table of Contents**USE OF PROCEEDS**

We will have broad discretion in the use of the net proceeds from any sale of securities offered under this prospectus. We intend to use the net proceeds for working capital and general corporate purposes, which include, but are not limited to, the funding of clinical development of and pursuing regulatory approval for our product candidates, general and administrative expenses, and the acquisition of companies, businesses or assets.

We have not determined the amount of net proceeds to be used specifically for such purposes. Pending the use of any net proceeds, we expect to invest the net proceeds in interest-bearing, marketable securities.

DILUTION

If you purchase shares of our common stock upon the exercise of your warrant, your ownership interest will be diluted to the extent of the difference between the exercise price per share and the net tangible book value per share of our common stock immediately after giving effect to this offering.

The net tangible book value of our common stock as of December 31, 2014, was approximately \$47.1 million, or approximately \$0.30 per share. Net tangible book value per share represents the amount of our total tangible assets, less the amount of our total tangible liabilities, divided by the total number of shares of our common stock outstanding. Dilution per share to new investors represents the difference between the amount per share paid by purchasers for each share of common stock in this offering and the net tangible book value per share of our common stock immediately following the completion of this offering, assuming the pre-funded warrants and warrants are fully exercised.

After giving effect to the sale of 35,092,693 shares of our common stock to investors exercising pre-funded warrants and warrants for cash (pre-funded warrants to purchase 13,081,428 shares of our common stock at an exercise price of \$0.01 per share, and warrants to purchase 22,011,265 shares of our common stock at an exercise price of \$0.75 per share), the as-adjusted net tangible book value of our common stock as of December 31, 2014 would have been approximately \$63.7 million, or approximately \$0.37 per share. This represents an immediate increase in net tangible book value of approximately \$0.07 per share to our existing stockholders and an immediate dilution in as-adjusted net tangible book value of approximately \$0.38 per share to investors exercising warrants, as illustrated by the following table:

Exercise price per share of the warrants	\$ 0.75
Net tangible book value per share as of December 31, 2014	\$ 0.30
Increase per share attributable to this offering	\$ 0.07
As-adjusted net tangible book value per share as of December 31, 2014, after giving effect to this offering	\$ 0.37
Dilution per share to investors purchasing shares in this offering upon exercise of warrants	\$ 0.38

Investors exercising pre-funded warrants for cash would not experience immediate dilution because the exercise price of the pre-funded warrants is \$0.01 per share.

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

The table above assumes, for illustrative purposes only, that all 35,092,693 shares of our common stock are sold in this offering upon the exercise of pre-funded warrants and warrants for cash for aggregate gross proceeds of \$16.6 million.

Table of Contents

The table above is based on 159,458,376 shares of our common stock outstanding as of December 31, 2014 and excludes:

44,056,875 shares of our common stock issuable upon exercise of warrants outstanding as of December 31, 2014, with a weighted-average exercise price of \$1.01 per share;

13,616,137 shares of our common stock issuable upon exercise of options outstanding as of December 31, 2014, with a weighted-average exercise price of \$1.00 per share;

10,388,691 shares and 306,945 shares of our common stock available for future grants under our 2014 Omnibus Incentive Plan and 2005 Employee Stock Purchase Plan as of December 31, 2014, respectively; and

12,478,050 shares of common stock that may be issued to the former stockholders of SynthRx, Inc., subject to the achievement of performance milestones, pursuant to the terms of the merger agreement with SynthRx. In addition, the discussion and table above exclude the up to approximately \$14,651,207 million of shares of our common stock that remained available for sale at March 24, 2015, under our sales agreement with Cowen and Company, LLC.

To the extent that any outstanding options or warrants are exercised, new options are issued under our equity incentive plan, shares of common stock are sold under our employee stock purchase plan or we otherwise issue additional shares of common stock, including under the sales agreement with Cowen and Company, LLC, in the future at prices per share below the price per share for any shares sold in this offering upon exercise of warrants, there will be further dilution to new investors.

DESCRIPTION OF COMMON STOCK

The following description of our common stock, together with any additional information we include in any free writing prospectus, summarizes the material terms and provisions of our common stock offered under this prospectus. For the complete terms of our common stock, please refer to our certificate of incorporation and our amended and restated bylaws, or bylaws, that are incorporated by reference into the registration statement of which this prospectus is a part or may be incorporated by reference in this prospectus. The terms of our common stock may also be affected by the Delaware General Corporation Law, or the DGCL. The summary below and that contained in any free writing prospectus are qualified in their entirety by reference to our certificate of incorporation and bylaws, as in effect at the time of any offering of securities under this prospectus.

Common Stock

As of the date of this prospectus, our certificate of incorporation authorizes us to issue 500,000,000 shares of common stock, par value \$0.001 per share, of which 159,458,376 shares were issued and outstanding as of March 20, 2015. Additional shares of authorized common stock may be issued, as authorized by our board of directors from time to time, without stockholder approval, except as may be required by applicable securities exchange requirements. The holders of common stock possess exclusive voting rights in us, except to the extent our board of directors specifies

voting power with respect to any other class of securities issued in the future. Each holder of our common stock is entitled to one vote for each share held of record on each matter submitted to a vote of stockholders, including the election of directors. Stockholders do not have any right to cumulate votes in the election of directors.

Subject to preferences that may be granted to the holders of preferred stock, each holder of our common stock is entitled to share ratably in distributions to stockholders and to receive ratably such dividends as may be declared by our board of directors out of funds legally available therefor. In the event of our liquidation, dissolution or winding up, the holders of our common stock will be entitled to receive, after payment of all of our

Table of Contents

debts and liabilities and of all sums to which holders of any preferred stock may be entitled, the distribution of any of our remaining assets. Holders of our common stock have no conversion, exchange, sinking fund or redemption rights and have no preemptive rights to subscribe for any of our securities.

All of the outstanding shares of our common stock are fully paid and non-assessable. The shares of common stock offered by this prospectus, when issued and paid for, will also be, fully paid and non-assessable.

Securities Exchange Listing

Our common stock is listed on the NYSE MKT under the symbol MSTX.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company.

Anti-Takeover Effects of Provisions of our Charter Documents and Delaware Law

Provisions of the DGCL, our certificate of incorporation and our bylaws, as amended to date, could make it more difficult to acquire us by means of a tender offer, a proxy contest or otherwise, or to remove incumbent officers and directors. These provisions, summarized below, are expected to discourage certain types of coercive takeover practices and takeover bids that our board of directors may consider inadequate and to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of increased protection of our ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging takeover or acquisition proposals because, among other things, negotiation of these proposals could result in an improvement of their terms. This summary does not purport to be complete and is qualified in its entirety by reference to the DGCL and our certificate of incorporation and bylaws.

Certificate of Incorporation and Bylaws

Preferred Stock. Under our certificate of incorporation, our board of directors has the power to authorize the issuance of up to 1,000,000 shares of preferred stock, all of which are currently undesignated, and to determine the price, rights, preferences, privileges and restrictions, including voting rights, of those shares without further vote or action by our stockholders. The issuance of preferred stock may:

delay, defer or prevent a change in control;

discourage bids for our common stock at a premium over the market price of our common stock;

adversely affect the voting and other rights of the holders of our common stock; and

discourage acquisition proposals or tender offers for our shares and, as a consequence, inhibit fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Advance Notice Requirement. Stockholder nominations of individuals for election to our board of directors and stockholder proposals of other matters to be brought before an annual meeting of our stockholders must comply with the advance notice procedures set forth in our bylaws. Generally, to be timely, such notice must be received at our principal executive offices no later than the date specified in our proxy statement released to stockholders in connection with the preceding year's annual meeting of stockholders, which date shall be not earlier than the 120th day, nor later than the close of business on the 90th day, prior to the first anniversary of the date of the preceding year's annual meeting of stockholders.

Table of Contents

Special Meeting Requirements. Our bylaws provide that special meetings of our stockholders may be called only at the request of our board of directors, president (unless there is a chief executive officer who is not the president, in which case a special meeting may be called at any time by the chief executive officer and not the president) or chair of the board of directors. Only such business shall be considered at a special meeting as shall have been stated in the notice for such meeting.

No Cumulative Voting. Our certificate of incorporation does not include a provision for cumulative voting for directors.

Indemnification. Our certificate of incorporation and bylaws provide that we will indemnify our officers and directors against losses as they incur in investigations and legal proceedings resulting from their services to us, which may include service in connection with takeover defense measures.

Removal of Directors. Our bylaws provide that the affirmative vote of the holders of at least 75% of our voting stock then outstanding is required to remove our directors, either with or without cause.

Authorized but Unissued Shares. Our authorized but unissued shares of common stock and preferred stock will be available for future issuance without stockholder approval. We may use additional shares for a variety of purposes, including future public offerings to raise additional capital, to fund acquisitions and as employee compensation. The existence of authorized but unissued shares of common stock and preferred stock could render more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the DGCL, an anti-takeover law. In general, Section 203 prohibits, with some exceptions, a publicly held Delaware corporation from engaging in a business combination with any interested stockholder for a period of three years following the date that stockholder became an interested stockholder, unless:

prior to that date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;

upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the number of shares of voting stock outstanding (but not the voting stock owned by the interested stockholder) those shares owned by persons who are directors and officers and by excluding employee stock plans in which employee participants do not have the right to determine whether shares held subject to the plan will be tendered in a tender or exchange offer; or

on or subsequent to that date, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66-2/3% of the outstanding voting stock that is not owned by the interested stockholder.

Section 203 defines business combination to include any of the following:

any merger or consolidation involving the corporation and the interested stockholder;

any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;

subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

Table of Contents

any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or

the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any person who, together with the person's affiliates and associates, beneficially owns, or within three years prior to the determination of interested stockholder status did beneficially own, 15% or more of the outstanding voting stock of the corporation.

The above provisions may deter a hostile takeover or delay a change in control of management or us.

PLAN OF DISTRIBUTION

The common stock offered under this prospectus will be offered solely by us and will be issued and sold upon the exercise of the warrants described in this prospectus. The warrant holders must surrender payment in cash of the aggregate exercise price of the shares being acquired upon exercise of the warrants. If, however, we are unable to offer and sell the shares underlying the warrants pursuant to this prospectus due to the ineffectiveness of the registration statement of which this prospectus is a part, then the warrants may only be exercised on a net or cashless basis. In addition, any time after two years from the date of original issuance of the warrants, a holder may, in its discretion, elect to exercise the warrants on a net or cashless basis. No fractional shares of common stock will be issued in connection with the exercise of a warrant. In lieu of fractional shares, we will pay the holder an amount in cash equal to the fractional amount multiplied by the exercise price.

LEGAL MATTERS

DLA Piper LLP (US), San Diego, California, has passed upon the validity of the common stock offered by this prospectus.

EXPERTS

The consolidated financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2014 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of such firm as experts in auditing and accounting.

INFORMATION INCORPORATED BY REFERENCE

The SEC allows us to incorporate by reference into this prospectus the information we file with the SEC. This means that we can disclose important information to you by referring you to those documents. Any statement contained in a document incorporated by reference in this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained herein, or in any subsequently filed document, which also is incorporated by reference herein, modifies or supersedes such earlier statement. Any such statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

Table of Contents

We hereby incorporate by reference into this prospectus the following documents that we have filed with the SEC under the Exchange Act File No. 001-32157 (other than current reports on Form 8-K, or portions thereof, furnished under Items 2.02 or 7.01 of Form 8-K):

our Annual Report on Form 10-K for the fiscal year ended December 31, 2014, filed with the SEC on March 24, 2015;

our Current Reports on Form 8-K filed with the SEC on January 6, 2015, January 7, 2015, January 12, 2015, January 27, 2015, February 3, 2015, February 9, 2015, and March 2, 2015; and

the description of our common stock contained in our registration statement on Form 8-A filed with the SEC on April 27, 2004 (File No. 001-32157-041020580).

All documents that we file with the SEC pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than current reports on Form 8-K, or portions thereof, furnished under Items 2.02 or 7.01 of Form 8-K) (i) after the initial filing date of the registration statement of which this prospectus forms a part and prior to the effectiveness of such registration statement and (ii) after the date of this prospectus and prior to the termination of the offering shall be deemed to be incorporated by reference in this prospectus from the date of filing of the documents, unless we specifically provide otherwise. Information that we file with the SEC will automatically update and may replace information previously filed with the SEC. To the extent that any information contained in any current report on Form 8-K or any exhibit thereto, was or is furnished to, rather than filed with the SEC, such information or exhibit is specifically not incorporated by reference.

Upon written or oral request made to us at the address or telephone number below, we will, at no cost to the requester, provide to each person, including any beneficial owner, to whom this prospectus is delivered, a copy of any or all of the information that has been incorporated by reference in this prospectus (other than an exhibit to a filing, unless that exhibit is specifically incorporated by reference into that filing), but not delivered with this prospectus. You may also access this information on our website at www.masttherapeutics.com by viewing the SEC Filings subsection of the Investors menu. No additional information on our website is deemed to be part of or incorporated by reference into this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

Mast Therapeutics, Inc.

3611 Valley Centre Drive, Suite 500

San Diego, CA 92130

Attn: Investor Relations

(858) 552-0866

WHERE YOU CAN FIND MORE INFORMATION

As permitted by SEC rules, this prospectus omits certain information that is included in the registration statement of which this prospectus forms a part and its exhibits. Since this prospectus may not contain all of the information that

you may find important, you should review the full text of these documents. If we have filed a contract, agreement or other document as an exhibit to the registration statement of which this prospectus forms a part, you should read the exhibit for a more complete understanding of the document or matter involved. Each statement in this prospectus, including statements incorporated by reference as discussed above, regarding a contract, agreement or other document is qualified in its entirety by reference to the actual document.

We are subject to the information reporting requirements of the Exchange Act, and, in accordance with these requirements, we file annual, quarterly and current reports, proxy statements, and other information with the SEC. You may inspect, read and copy the reports and other information we file with the SEC at the SEC s

Table of Contents

Public Reference Room located at 100 F Street, N.E., Washington, D.C. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an internet website at <http://www.sec.gov> that contains our filed reports, proxy and information statements, and other information that we file electronically with the SEC. Additionally, we make these filings available, free of charge, on our website at www.masttherapeutics.com in the SEC Filings subsection of the Investors menu as soon as reasonably practicable after we electronically file such materials with, or furnish them to, the SEC. The information on our website, other than these filings, is not, and should not be, considered part of this prospectus, is not incorporated by reference into this prospectus, and should not be relied upon in connection with making any investment decision with respect to our securities.

Table of Contents

13,081,428 Shares of Common Stock Underlying Pre-Funded Warrants

22,011,265 Shares of Common Stock Underlying Warrants

PROSPECTUS

, 2015

Table of Contents

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. *Other Expenses of Issuance and Distribution*

The following table sets forth the fees and expenses incurred or expected to be incurred by us in connection with the issuance and distribution of the securities being registered hereby, other than underwriting discounts and commissions.

SEC registration fee*	\$ 19,364
NYSE MKT listing application fees	**
Transfer agent fees and expenses	**
FINRA filing fees	**
Legal fees and expenses	**
Accounting fees and expenses	**
Printing fees and engraving expenses	**
Miscellaneous expenses	**
Total	**

* Includes the \$13,024 previously paid in connection with unsold securities pursuant to Rule 415(a)(6).

** These fees or expenses cannot be estimated at this time, as they are calculated based on the securities offered and the number of issuances. An estimate of the aggregate expenses in connection with the sale and distribution of the securities being offered will be included in the applicable prospectus supplement.

Item 15. *Indemnification of Directors and Officers*

Section 145 of the Delaware General Corporation Law authorizes a corporation to indemnify its directors and officers against liabilities arising out of actions, suits and proceedings to which they are made or threatened to be made a party by reason of the fact of their prior or current service to the corporation as a director or officer, in accordance with the provisions of Section 145, which are sufficiently broad to permit indemnification under certain circumstances for liabilities arising under the Securities Act of 1933, as amended (the "Securities Act"). The indemnity may cover expenses (including attorneys' fees) judgments, fines and amounts paid in settlement actually and reasonably incurred by the director or officer in connection with any such action, suit or proceeding. Section 145 permits corporations to pay expenses (including attorneys' fees) incurred by directors and officers in advance of the final disposition of such action, suit or proceeding. In addition, Section 145 provides that a corporation has the power to purchase and maintain insurance on behalf of its directors and officers against any liability asserted against them and incurred by them in their capacity as a director or officer, or arising out of their status as such, whether or not the corporation would have the power to indemnify the director or officer against such liability under Section 145.

Our amended and restated certificate of incorporation, as amended (our Certificate of Incorporation), provides that, to the fullest extent permitted by the Delaware General Corporation Law, (1) a director shall not be personally liable to us or our stockholders for monetary damages for breach of fiduciary duty as a director, and (2) we shall indemnify any director or officer made a party to an action or proceeding, whether criminal, civil, administrative or investigative, by reason of the fact of such person's current or prior service as our director or officer, as a director or officer of any of our predecessors or any other enterprise per our or any of our predecessor's request.

II-1

Table of Contents

Our amended and restated bylaws, as amended (our Bylaws), provide that (a) we shall indemnify our directors and officers to the maximum extent and in the manner permitted by the Delaware General Corporation Law against expenses (including attorneys fees), judgments, fines, ERISA excise taxes, settlements and other amounts actually and reasonably incurred in connection with any proceeding, whether civil, criminal, administrative or investigative, arising by reason of the fact that such person is or was an agent of the corporation, subject to certain limited exceptions, (b) we shall advance expenses incurred by any director or officer prior to the final disposition of any proceeding to which the director or officer was or is or is threatened to be made a party promptly following a request therefore, subject to certain limited exceptions, and (c) the rights conferred in our Bylaws are not exclusive.

We have entered into indemnification agreements with each of our directors and executive officers to give such directors and officers additional contractual assurances regarding the scope of the indemnification set forth in our Certificate of Incorporation and Bylaws and to provide additional procedural protections. These agreements, among other things, provide that we will indemnify our directors and executive officers for expenses (including attorneys fees), judgments, fines, penalties and amounts paid in settlement (including all interest, assessments and other charges paid or payable in connection therewith) actually and reasonably incurred by a director or executive officer in connection with any action or proceeding to which such person was, is or is threatened to be made a party, a witness or other participant by reason of such person's services as our director or executive officer, or as a director or executive officer of any of our subsidiaries or any other company or enterprise to which the person provides services at our request, and any federal, state, local or foreign taxes imposed on the director or executive officer as a result of the actual or deemed receipt of any payments under the indemnification agreements.

In addition, the indemnification agreements provide that, upon the request of a director or executive officer, we shall advance expenses (including attorneys fees) to the director or officer. We intend to enter into indemnification agreements with any new directors and executive officers in the future.

We have also obtained an insurance policy covering our directors and officers with respect to certain liabilities, including liabilities arising under the Securities Act.

Item 16. Exhibits

The list of exhibits in the Exhibit Index to this registration statement is incorporated herein by reference.

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

- (ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20 percent change in the maximum aggregate offering price set forth in the Calculation of Registration Fee table in the effective registration statement; and

II-2

Table of Contents

- (iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

Provided, however, that paragraphs (a)(1)(i), (a)(1)(ii) and (a)(1)(iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement;

- (2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof;
- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering;
- (4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:
 - (A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and
 - (B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5) or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii) or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which the prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date; and

(5)

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities, the undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

- (i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;
- (ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned Registrant or used or referred to by the undersigned registrant;

II-3

Table of Contents

- (iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of an undersigned registrant; and
 - (iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.
- (b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to section 13(a) or section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.
- (c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Act and will be governed by the final adjudication of such issue.
- (d) The undersigned registrant hereby undertakes that:
 - (1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.
 - (2) For the purpose of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.
- (e) The undersigned registrant hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Commission under Section 305(b)(2) of the Act.

Table of Contents**SIGNATURES**

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of San Diego, State of California, on March 24, 2015.

MAST THERAPEUTICS, INC.

By: /s/ Brandi L. Roberts
 Brandi L. Roberts
*Chief Financial Officer and
 Senior Vice President*

Power of Attorney

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Brian M. Culley and Brandi L. Roberts, and each of them acting individually, as his or her true and lawful attorneys-in-fact and agent, with full power of each to act alone, with full powers of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments to this registration statement (including post-effective amendments and any related registration statements filed pursuant to Rule 462 and otherwise), 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, and 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 or she might or could do in person, hereby ratifying and confirming that all 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 Act of 1933, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Brian M. Culley Brian M. Culley	Chief Executive Officer and Director (<i>Principal Executive Officer</i>)	March 24, 2015
/s/ Brandi L. Roberts Brandi L. Roberts	Chief Financial Officer and Senior Vice President (<i>Principal Financial and Accounting Officer</i>)	March 24, 2015
/s/ Jack Lief Jack Lief	Chair of the Board	March 24, 2015
/s/ Howard Dittrich	Director	March 24, 2015

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

Howard Dittrich

/s/ David A. Ramsay

Director

March 24, 2015

David A. Ramsay

/s/ Lewis J. Shuster

Director

March 24, 2015

Lewis J. Shuster

Table of Contents**EXHIBIT INDEX**

Exhibit Number	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
1.1*	Form of Underwriting Agreement				
1.2	Sales Agreement, dated February 10, 2014, between the registrant and Cowen and Company, LLC		Form 8-K	001-32157-14586244	02/10/14
3.1	Composite Amended and Restated Certificate of Incorporation, as amended, of the registrant		Form S-1	333-188870-13873232	05/28/13
3.2	Composite Amended and Restated Bylaws, as amended, of the registrant		Form 10-K	001-32157-14717498	03/26/14
4.1	Form of common stock certificate of the registrant		Form 10-K	001-32157-13702619	03/19/13
4.2	Form of Pre-Funded Warrant Agent Agreement, dated as of November 6, 2014, between the registrant and American Stock Transfer & Trust Company, LLC		Form 8-K	001-32157-141202528	11/07/14
4.3	Form of Pre-Funded Warrant issued by the registrant on November 12, 2014		Form 8-K	001-32157-141202528	11/07/14
4.4	Form of Warrant Agent Agreement, dated as of November 6, 2014 between the registrant and American Stock Transfer & Trust Company, LLC		Form 8-K	001-32157-141202528	11/07/14
4.5	Form of Warrant issued by the registrant on November 12, 2014		Form 8-K	001-32157-141202528	11/07/14
4.6	Form of Senior Indenture	X			
4.7	Form of Subordinated Indenture	X			
4.8*	Form of Senior Note				
4.9*	Form of Subordinated Note				
4.10*	Form of Warrant				
4.11*	Form of Unit Agreement				

Edgar Filing: Mast Therapeutics, Inc. - Form S-3

4.12*	Form of Preferred Stock Certificate	
4.13*	Form of Certificate of Designation with respect to Preferred Stock	
5.1	Opinion of DLA Piper LLP	X
23.1	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm	X
23.2	Consent of DLA Piper LLP (US) (included in Exhibit 5.1)	X
24.1	Power of attorney (included on the signature page to the registration statement)	X

Table of Contents

Exhibit Number	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
25.1**	Statement of Eligibility on Form T-1 under the Trust Indenture Act of 1939, as amended, of the Trustee under the Senior Indenture				
25.2**	Statement of Eligibility on Form T-1 under the Trust Indenture Act of 1939, as amended, of the Trustee under the Subordinated Indenture				

* To be filed by amendment or as an exhibit to a report pursuant to Section 13(a), 13(c) or 15(d) of the Exchange Act

** To be filed pursuant to Section 305(b)(2) of the Trust Indenture Act of 1939