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

**AMENDMENT NO. 1
TO
POST-EFFECTIVE AMENDMENT NO. 5
TO
FORM S-1 ON 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)

**12390 El Camino Real, Suite 150
San Diego, CA 92130
(858) 552-0866**

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

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President and Chief Operating Officer
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(858) 552-0866**

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

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

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

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.

Explanatory Note

Pursuant to Rule 429(a) under the Securities Act of 1933, as amended (the “**Securities Act**”), the prospectus contained in this Amendment No.1 to Post-Effective Amendment No. 5 to Form S-1 on Form S-3 filed on March 26, 2014 (this “**Amendment to Post-Effective Amendment No. 5**”) will be used as a combined prospectus in connection with the following registration statements (collectively, the “**Prior Registration Statements**”):

- Registration Statement on Form S-1 originally filed with the Securities and Exchange Commission (the “**SEC**”) on July 24, 2009 (File No. 333-160778), as amended by Amendment Nos. 1, 2 and 3 thereto filed with the SEC on September 3, 2009, September 25, 2009 and October 5, 2009, respectively, which was declared effective on October 6, 2009, registering the offer and sale of 11,283 shares of the registrant’s 4.25660% Series D Convertible Preferred Stock, warrants to purchase up to 19,800,000 shares of the registrant’s common stock, and 79,800,000 shares of the registrant’s common stock issuable upon conversion and exercise of such shares of preferred stock and warrants, respectively, and which was further amended by Post-Effective Amendment No. 1 thereto filed with the SEC on March 18, 2010, which was declared effective on March 23, 2010, which was further amended by Post-Effective Amendment Nos. 2, 3 and 4 thereto filed with the SEC on March 10, 2011, April 28, 2011 and May 10, 2011, respectively, which was declared effective on May 11, 2011 (collectively, the “**Prior Post-Effective Amendments**”).
- Registration Statement on Form S-1 originally filed with the SEC on October 6, 2009 (File No. 333-162361) pursuant to Rule 462(b) under the Securities Act for the sole purpose of registering additional securities of the same class as were included in the Registration Statement on Form S-1 (File No. 333-160778) described in the paragraph above, and which was further amended by the Prior Post-Effective Amendments (collectively, Registration Statement on Form S-1 (File No. 333-162361) and Registration Statement on Form S-1 (File No. 333-160778), in each case, as amended by the Prior Post-Effective Amendments, the “**2009 Registration Statement**”).
- Registration Statement on Form S-1 originally filed with SEC on May 28, 2013 (File No. 333-188870), as amended by Amendment Nos. 1, 2 and 3 thereto filed with the SEC on June 5, 2013, June 13, 2013 and June 14, 2013, respectively, which was declared effective on June 14, 2013, registering the offer and sale of 50,000,000 units, with each unit consisting of one share of the registrant’s common stock and one warrant to purchase 0.5 of a share of the registrant’s common stock, and the shares of the registrant’s common stock issuable from time to time upon exercise of such warrants (the “**2013 Registration Statement**”).

In addition to the shares of common stock discussed above, pursuant to Rule 416 under the Securities Act, the Prior Registration Statements also registered an indeterminate number of shares of common stock as may be issuable with respect to the shares being registered thereunder as a result of stock splits, stock dividends or similar transactions.

All of the securities registered for offer and sale by the registrant under the Prior Registration Statements have been offered and sold other than shares of the registrant’s common stock issuable upon exercise of certain outstanding warrants that were originally registered under and issued pursuant to the Prior Registration Statements.

Post-Effective Amendment No. 5 to the Prior Registration Statements was filed to convert each of the Prior Registration Statements into registration statements on Form S-3 and to update each of the Prior Registration Statements pursuant to Section 10(a)(3) of the Securities Act to include an updated prospectus relating to the offer and sale of shares of the registrant’s common stock upon exercise of the warrants that were originally registered under and issued pursuant to the Prior Registration Statements and that remain outstanding. This Amendment to Post-Effective Amendment No. 5 is being filed to file an updated consent of PricewaterhouseCoopers LLP, the Company’s independent registered public accounting firm.

Accordingly, this Amendment to Post-Effective Amendment No. 5 continues the registration of:

- 216,000 shares of the registrant’s common stock issuable upon exercise of an outstanding warrant that was originally registered under and issued pursuant to the 2009 Registration Statement; and
- 28,097,500 shares of the registrant’s common stock issuable upon exercise of outstanding warrants that were originally registered under and issued pursuant to the 2013 Registration Statement.

No additional securities are being registered under this Amendment to Post-Effective Amendment No. 5. All applicable registration fees were paid at the time of the original filing of the Prior Registration Statements, as applicable.

Pursuant to Rule 429(b) under the Securities Act, the prospectus included in this Amendment to Post-Effective Amendment No. 5 is a combined prospectus for each of the Prior Registration Statements, and this Amendment to Post-Effective Amendment No. 5 constitutes a post-effective amendment to each of the Prior Registration Statements (File Nos. 333-160778, 333-162361 and 333-188870).

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 MAY 5, 2014

PRELIMINARY PROSPECTUS



Up to 28,313,500 Shares of Common Stock Issuable upon Exercise of Outstanding Warrants

This prospectus relates to the issuance of up to 28,313,500 shares of our common stock upon the exercise of outstanding warrants that we issued in registered offerings described below:

- In October 2009, we completed an offering of 11,283 shares of our convertible preferred stock and warrants to purchase up to 792,000 shares of our common stock. All 11,283 shares of the convertible preferred stock have been converted into shares of our common stock and all of the warrants have been exercised other than one warrant to purchase up to 216,000 shares of our common stock. This one warrant, which remains outstanding as of the date of this prospectus and which we refer to in this prospectus as the 2009 Warrant, has an exercise price of \$3.67 per share, and is exercisable at any time on or before October 9, 2014.

- In June 2013, we completed an offering of 56,195,000 shares of our common stock and warrants to purchase up to 28,097,500 shares of our common stock. These securities were offered and sold in units with each unit consisting of one share of common stock and one warrant to purchase up to 0.5 of a share of common stock. All of these warrants remain outstanding as of the date of this prospectus. These warrants, which we refer to in this prospectus as the 2013 Warrants, have an exercise price of \$0.65 per share, and are exercisable at any time on or before June 19, 2018.

Our common stock is listed on the NYSE MKT under the symbol "MSTX." On May 2, 2014, the closing sale price for our common stock was \$0.59 per share.

Investing in our securities involves a high degree of risk. Before buying any of our securities, see the section entitled "[Risk Factors](#)" on page 3 of this prospectus, and as updated in future filings we make with the Securities and Exchange Commission that are incorporated by reference into this prospectus. See "Information Incorporated by Reference."

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 _____, 2014

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the SEC. As permitted by SEC rules, that registration statement includes additional information not contained in this prospectus. You may read that 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 Additional Information.”

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. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus. This prospectus does not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which it relates, nor does this prospectus 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 is accurate on any date subsequent to the date set forth on the front of this prospectus, 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 is delivered or securities are sold on a later date.

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 prospectus, including the information contained under the heading “Risk Factors,” and all other information included or incorporated by reference into this prospectus, in its entirety before you invest in our securities.

References to “we,” “us,” “our,” “our company,” “the Company,” and “Mast” refers to Mast Therapeutics, Inc. and its subsidiaries, unless the context requires otherwise.

Company Overview

We are a biopharmaceutical company developing novel therapies for serious or life-threatening diseases with significant unmet needs. We are leveraging our Molecular Adhesion & Sealant Technology, or MAST, platform, derived from over two decades of clinical, nonclinical and manufacturing experience with purified and non-purified poloxamers, to develop MST-188, our lead product candidate. MST-188 has demonstrated multiple pharmacologic effects that may provide clinical benefit in a wide range of diseases and conditions typically characterized by impaired microvascular blood flow and damaged cell membranes. We recently acquired Aires Pharmaceuticals, Inc., which is developing AIR001 (sodium nitrite) inhalation solution, and we are in the process of determining the optimal development strategy for this new asset.

We have devoted substantially all of our resources to research and development and to acquisition of our product candidates. We have not yet marketed or sold any products or generated any significant revenue and, as of March 31, 2014, we have incurred a total of \$208.1 million of operating losses since inception. Our cash, cash equivalents and investment securities were \$49.6 million as of March 31, 2014.

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

Corporate Information

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

Our principal executive offices are located at 12390 El Camino Real, Suite 150, San Diego, CA 92130 and our telephone number at that address is (858) 552-0866.

THE OFFERING

Securities offered	<p>Up to 28,313,500 shares of our common stock upon the exercise of the following outstanding warrants that we issued in prior registered offerings:</p> <ul style="list-style-type: none">• one warrant to purchase up to 216,000 shares of our common stock, which is exercisable at any time on or before October 9, 2014 and which we issued and sold in a registered offering completed in October 2009; and• warrants to purchase up to 28,097,500 shares of our common stock, which are exercisable at any time on or before June 19, 2018 and which we issued and sold in a registered offering completed in June 2013. <p>In this prospectus, we refer: (i) to the warrant we issued and sold in October 2009 as the 2009 Warrant, (ii) to the warrants we issued and sold in June 2013 as the 2013 Warrants, and (iii) to the 2009 Warrant and the 2013 Warrants, collectively, as the 2009 and 2013 Warrants.</p>
Exercise price	<p>The exercise price of the 2009 Warrant is \$3.67 per share and the exercise price of the 2013 Warrants is \$0.65 per share, in each case, subject to adjustment in the event of stock splits, stock dividends, combinations and similar events affecting our common stock.</p>
Use of proceeds	<p>If all of the 2009 and 2013 Warrants are exercised in full and the exercise price therefor is paid in cash, we will receive approximately \$19.1 million in proceeds. However, the timing of the exercise and the extent to which any of the 2009 and 2013 Warrants are exercised are beyond our control. We plan to use the net proceeds from the exercise of the 2009 and 2013 Warrants, if any, for working capital and general corporate purposes, which include, but are not limited to, the funding of research and product development activities, including our ongoing and future nonclinical and clinical trials, and general and administrative expenses. See “Use of Proceeds” on page 5.</p>
Risk factors	<p>See “Risk Factors” on page 3, 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 securities.</p>
Shares of common stock outstanding after this offering	<p>142,035,147 shares if all of the 2009 and 2013 Warrants are exercised in full and the exercise price therefor is paid in cash.</p>
NYSE MKT Symbol	<p>MSTX</p>

The number of shares of our common stock outstanding after this offering as shown above assumes that all of the 2009 and 2013 Warrants are exercised in full and the exercise price therefor is paid in cash, and is based on 113,721,647 shares of our common stock outstanding as of March 31, 2014 and excludes, as of March 31, 2014:

- 16,272,432 shares of our common stock issuable upon exercise of outstanding warrants (other than the 2009 and 2013 Warrants), with a weighted-average exercise price of \$1.77 per share;
- 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;
- 4,198,830 shares of common stock that will be issued to the former stockholders of Aires Pharmaceuticals, Inc., subject to adjustment to satisfy indemnification obligations of the former Aires stockholders in accordance with the terms of the merger agreement with Aires;
- 9,491,728 shares of our common stock issuable upon exercise of outstanding options, with a weighted-average exercise price of \$1.18 per share; and
- 1,064,322 shares and 276,945 shares of our common stock available for future grants under our 2013 Omnibus Incentive Plan and 2005 Employee Stock Purchase Plan, respectively.

In addition, the number of shares of our common stock outstanding after this offering as shown above excludes shares of our common stock that we may sell and issue after March 31, 2014, from time to time, in an ongoing “at the market” equity offering program, or ATM program. Under the ATM program, we may sell shares of our common stock through a sales agent, Cowen and Company, LLC, for aggregate gross proceeds of up to \$30 million. As of March 31, 2014, we had sold and issued 9,961,655 shares under the ATM program for aggregate gross proceeds of \$8.3 million.

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, 2013, which are 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 Securities Exchange Act of 1934, as amended, or the Exchange Act, before deciding whether to invest in our securities. 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 those 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.

CAUTIONARY 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. The words “believe,” “anticipate,” “estimate,” “plan,” “expect,” “intend,” “may,” “could,” “should,” “potential,” “likely,” “projects,” “continue,” “will,” and “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will achieve the plans, intentions or expectations expressed in our forward-looking statements and you should not place undue reliance on our forward-looking 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 set forth above under “Risk Factors.” 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.

DESCRIPTION OF SECURITIES

The following description of our capital stock and the 2009 and 2013 Warrants summarizes the material terms and provisions thereof. The shares of our common stock issued upon the exercise, if any, of the 2009 and 2013 Warrants will be issued pursuant to the warrants between each of the investors and us. For the complete terms of our capital stock and the terms and conditions applicable to the 2009 and 2013 Warrants, please refer to our amended and restated certificate of incorporation and our amended and restated bylaws, as amended, and the forms of the 2009 Warrant and the 2013 Warrant, which we filed as exhibits to the registration statement of which this prospectus is a part. The summary below is qualified in its entirety by reference to our amended and restated certificate of incorporation and our amended and restated bylaws, as amended, and the forms of the 2009 Warrant and 2013 Warrant. The terms of these securities may also be affected by Delaware General Corporation Law.

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 114,136,502 shares were issued and outstanding as of April 30, 2014. 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, redemption or appraisal rights (other than such as may be determined by our board of directors in its sole discretion) 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 upon exercise of the 2009 and 2013 Warrants, when issued and paid for in accordance with the terms of the 2009 and 2013 Warrants, as applicable, will also be, fully paid and non-assessable.

Securities Exchange Listing

Our common stock is traded 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, LLC.

Preferred Stock

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.

The General Corporate Law of the State of Delaware, the state of our incorporation, 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.

The 2009 and 2013 Warrants

The 2009 Warrant was issued in a registered offering completed in October 2009 pursuant to a prospectus dated October 6, 2009. In that offering we offered and sold 11,283 shares of our 4.25660% Series D Convertible Preferred Stock and warrants to purchase up to 792,000 shares of our common stock. In addition, pursuant to that prospectus, as subsequently supplemented, 3,192,000 shares of our common stock issuable upon conversion of the convertible preferred stock and exercise of the warrants were registered to permit their issuance by us to the purchasers of our convertible preferred stock and warrants. All 11,283 shares of the convertible preferred stock have been converted into shares of our common stock. We did not receive any proceeds upon conversion of the convertible preferred stock. Warrants to purchase 576,000 shares of our common stock have been exercised and such warrants are no longer outstanding. The only warrant that remains outstanding from that offering as of the date of this prospectus is the 2009 Warrant, which entitles the holder to purchase up to 216,000 shares of our common stock at an exercise price of \$3.67 per share and which is exercisable at any time on or before October 9, 2014.

The 2013 Warrants were issued in an underwritten public offering completed in June 2013 pursuant to a prospectus dated June 14, 2013. In that offering we offered and sold 56,195,000 shares of our common stock and warrants to purchase up to 28,097,500 shares of our common stock. These securities were offered and sold to the underwriters and the public in units with each unit consisting of one share of common stock and one warrant to purchase up to 0.5 of a share of common stock. All of the 2013 Warrants remain outstanding as of the date of this prospectus and entitle the holders thereof to purchase up to 28,097,500 shares of our common stock in the aggregate at an exercise price of \$0.65 per share and which are exercisable at any time on or before June 19, 2018.

Subject to limited exceptions, the holder of the 2009 Warrant does not have the right to exercise any portion of such warrant if the holder, together with its affiliates, would beneficially own in excess of 4.99% of the number of shares of our common stock outstanding immediately after the exercise. Similarly, the holders of the 2013 Warrants do not have the right to exercise any portion of their warrant if the holder, together with its affiliates, would beneficially own in excess of 9.99% of the number of shares of our common stock outstanding immediately after the exercise.

The exercise prices of the 2009 and 2013 Warrants, and in some cases the number of shares issuable upon exercise thereof, are subject to adjustment in the event of stock splits, stock dividends, combinations, rights offerings and similar events affecting our common stock. In addition, in the event we consummate a fundamental corporate transaction such as a merger or consolidation with or into another person or other reorganization event in which our common stock is converted or exchanged for securities, cash or other property, or we sell, lease, license or otherwise dispose of all or substantially all of our assets or we or another person acquires 50% or more of our outstanding common stock, then following such event, the holders of the 2009 and 2013 Warrants will be entitled to receive, for each share that would have been issuable upon exercise of the 2009 and 2013 Warrants immediately prior to such fundamental transaction, the number of shares of common stock of the successor or acquiring corporation or of ours, if we are the surviving corporation, and any additional consideration receivable as a result of such fundamental transaction by a holder of the number of shares of common stock for which the 2009 and 2013 Warrants are exercisable immediately prior to such fundamental transaction. Any successor to us or surviving entity shall assume our obligations under the 2009 and 2013 Warrants.

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The holders of the 2009 and 2013 Warrants must surrender payment in cash of the aggregate exercise price of the shares being acquired upon exercise of the 2009 and 2013 Warrants. If, however, we are unable to offer and sell the shares underlying the 2009 and 2013 Warrants pursuant to this prospectus due to the registration statement of which this prospectus is a part not being effective, then the 2009 and 2013 Warrants may only be exercised on a “net” or “cashless” basis. No fractional shares of common stock will be issued in connection with the exercise of the 2009 and 2013 Warrants. In lieu of fractional shares, we will pay the holder an amount in cash equal to the fractional amount multiplied by the exercise price.

The 2009 and 2013 Warrants do not entitle the holders thereof to any voting rights, dividends or other rights as a stockholder of ours prior to the exercise of their 2009 and 2013 Warrants.

The 2009 and 2013 Warrants are not listed on, and we do not intend to list any of them on, any securities exchange or automated quotation system.

Warrant Agent

American Stock Transfer & Trust Company, LLC serves as our agent for the transfer, exchange, replacement and exercise of the 2013 Warrants.

We do not engage a third-party warrant agent for the transfer, exchange, replacement or exercise of the 2009 Warrant. The processing of such transactions is conducted directly by us.

USE OF PROCEEDS

If all of the 2009 and 2013 Warrants are exercised in full and the exercise price therefor is paid in cash, we will receive approximately \$19.1 million in proceeds. However, the timing of the exercise and the extent to which any of the 2009 and 2013 Warrants are exercised are beyond our control and depend on a number of factors, including the market price of our common stock. There can be no assurance that any of the 2009 and 2013 Warrants will be exercised, and it is possible that all of 2009 and 2013 Warrants may expire and may never be exercised. We will have broad discretion in the use of the net proceeds we receive from the exercise of the 2009 and 2013 Warrants, if any. We intend to use the net proceeds for working capital and general corporate purposes, which include, but are not limited to, the funding of research and product development activities, including our ongoing and future nonclinical and clinical trials, and general and administrative expenses. We may also use a portion of the net proceeds for strategic acquisitions of other companies, businesses or assets and/or evaluation of such opportunities from time to time.

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.

PLAN OF DISTRIBUTION

We are offering the shares of common stock issuable upon exercise of the 2009 and 2013 Warrants directly to the holders of the 2009 and 2013 Warrants, and such holders may purchase such shares of common stock directly from us by exercising their 2009 and 2013 Warrants in accordance with their terms.

LEGAL MATTERS

The validity of the 2009 and 2013 Warrants and the shares of our common stock issuable upon exercise of the 2009 and 2013 Warrants has been passed upon for us by DLA Piper LLP (US), San Diego, California.

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, 2013 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said 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, which 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):

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- our Annual Report on Form 10-K for the fiscal year ended December 31, 2013, filed with the SEC on March 26, 2014;
- the portions of our definitive proxy statement filed with the SEC on April 29, 2014 in connection with our 2014 annual meeting of stockholders that are incorporated by reference into Part III of our Annual Report on Form 10-K for the fiscal year ended December 31, 2013;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2014, filed with the SEC on May 5, 2014;
- our Current Reports on Form 8-K filed with the SEC on January 8, 2014, February 10, 2014, February 24, 2014, February 28, 2014, March 21, 2014 and March 26, 2014; 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.
12390 El Camino Real, Suite 150
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.



**Up to 28,313,500 Shares of Common Stock
Issuable upon Exercise of Outstanding Warrants**

PROSPECTUS

_____, 2014

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 the registrant in connection with the issuance and distribution of the securities being registered hereby. Such fees and expenses consist of both those incurred in connection with the issuance and distribution of the securities that have already occurred under the Prior Registration Statements (as such term is defined in the section entitled, “Explanatory Note,” above) and those expected to be incurred in the future in connection with the issuance of up to 28,313,500 shares of common stock upon the exercise of the 2009 and 2013 Warrants (as such term is defined in the prospectus of which this registration statement is a part). All of the amounts shown are estimated except the SEC registration fees, FINRA filing fees and NYSE MKT additional listing application fees.

SEC registration fees	\$ 10,041 (1)
Legal fees and expenses	\$285,000
Accounting fees and expenses	\$ 90,000
FINRA filing fees	\$ 10,850 (1)
NYSE MKT listing application fees	\$ 45,000 (1)
Transfer agent fees and expenses	\$ 5,000
Printing fees and engraving expenses	\$ 80,000
Miscellaneous expenses	\$ 4,109
Total	\$530,000

(1) Previously paid.

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 our predecessors or any other enterprise per our or any of our predecessor’s request.

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 of Mast, 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.

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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
 - (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 registration statement is on Form S-3 and 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

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- (5) 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;
 - (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.

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 May 5, 2014.

MAST THERAPEUTICS, INC.

By: /s/ Patrick L. Keran
Patrick L. Keran
President and Chief Operating Officer

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 date indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Brian M. Culley</u> Brian M. Culley	Chief Executive Officer and Director <i>(Principal Executive Officer)</i>	May 5, 2014
<u>/s/ Brandi L. Roberts</u> Brandi L. Roberts	Chief Financial Officer and Senior Vice President <i>(Principal Financial and Accounting Officer)</i>	May 5, 2014
<u>*</u> Jack Lief	Chair of the Board	May 5, 2014
<u>*</u> David A. Ramsay	Director	May 5, 2014
<u>*</u> Lewis J. Shuster	Director	May 5, 2014

*By: /s/ Patrick L. Keran
Patrick L. Keran, Attorney-in-Fact

EXHIBIT INDEX

Exhibit No.	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
2.1	Agreement and Plan of Merger, dated April 7, 2006, among the registrant, Speed Acquisition, Inc., SD Pharmaceuticals, Inc. and certain individuals named therein (including exhibits thereto)		Form 8-K/A	001-32157-06796248	05/01/06
2.2†	Agreement and Plan of Merger, dated February 12, 2011, by and among the registrant, SRX Acquisition Corporation, SynthRx, Inc. and, solely with respect to Sections 2 and 8, the Stockholders' Agent		Form 8-K	001-32157-11752769	04/11/11
2.3†	Agreement and Plan of Merger, dated February 7, 2014, by and among the registrant, AP Acquisition Sub, Inc., Aires Pharmaceuticals, Inc. and, solely with respect to Sections 2.8(b) and 6.3 and Article IX, the Stockholders' Representative, as amended by the Waiver of Closing Conditions, dated February 26, 2014		Form 10-Q		05/05/14
4.1	Composite Amended and Restated Certificate of Incorporation, as amended, of the registrant		Form S-1	333-188870-13873232	05/28/13
4.2	Composite Amended and Restated Bylaws, as amended, of the registrant		Form 10-K	001-32157-14717498	03/26/14
4.3	Form of common stock certificate of the registrant		Form 10-K	001-32157-13702619	03/19/13
4.4	Form of Securities Purchase Agreement		Form S-1/A	333-160778-091106385	10/05/09
4.5	Form of Common Stock Purchase Warrant		Form S-1/A	333-160778-091106385	10/05/09
4.6	Purchase Agreement by and between Mast Therapeutics, Inc. and Piper Jaffray & Co., on behalf of itself and the other several underwriters named in Schedule I thereto, dated June 14, 2013		Form 8-K	001-32157-13917371	06/17/13
4.7	Warrant Agent Agreement by and between Mast Therapeutics, Inc. and American Stock Transfer & Trust Company, dated June 14, 2013, including the form of Common Stock Purchase Warrant as Exhibit A		Form S-1/A	333-188870-13910357	06/23/13
5.1	Opinion of DLA Piper LLP (US)		Form S-1/A	333-160778-091087750	09/25/09
5.2	Opinion of DLA Piper LLP (US)		Form S-1	333-162361-091108489	10/06/09
5.3	Opinion of DLA Piper LLP (US)		Form S-1/A	333-188870-13910357	06/13/13

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Exhibit No.	Description	Filed Herewith	Incorporated by Reference		
			Form	File/Film No.	Date Filed
23.1	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm	X			
23.2	Consent of DLA Piper LLP (US) (included in Exhibit 5.1)		Form S-1/A	333-160778-091087750	09/25/09
23.3	Consent of DLA Piper LLP (US) (included in Exhibit 5.2)		Form S-1	333-162361-091108489	10/06/09
23.4	Consent of DLA Piper LLP (US) (included in Exhibit 5.3)		Form S-1/A	333-188870-13910357	06/13/13
24.1	Power of Attorney (included on signature page to Post-Effective Amendment No. 5 to Form S-1 on Form S-3 Registration Statement)		POS AM	333-188870-14718756	03/26/14

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

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in this Registration Statement on Form S-3 of our report dated March 26, 2014 relating to the financial statements, which appears in Mast Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2013. We also consent to the reference to us under the heading "Experts" in such Registration Statement.

/s/ PricewaterhouseCoopers LLP

San Diego, California
May 5, 2014