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

**AMENDMENT NO. 1
TO
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)

**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:
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4365 Executive Drive, Ste 1100
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Tel: (858) 677-1400
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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

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, \$111,511,176.22 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 \$111,511,176.22 (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 \$12,779.18 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 \$55,128,086.81 (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 \$12,779.18 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 with respect to the New Securities of \$6,157.21 was paid upon the initial filing of this registration statement on March 24, 2015. An additional filing fee with respect to the New Securities of \$248.67 is paid herewith.

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

This Amendment No. 1 (this “Amendment No. 1”) to the registration statement on Form S-3 (File No. 333-202960) of Mast Therapeutics, Inc. (the “Registration Statement”), is being filed solely for the purposes of modifying the amount of Unsold Securities to be included on the Registration Statement pursuant to Rule 415(a)(6), as indicated in footnote (6) of the “Calculation of Registration Fee” table of this Amendment No. 1, and updating the remaining amount available under the “at the market offering” prospectus. The aggregate amount of securities registered on the Registration Statement is unchanged by this Amendment No. 1.

The 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 \$12,511,176 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 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 shares of common stock that may be offered, issued and sold under the “at the market offering” prospectus are 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 \$12,511,176 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.

This Amendment No. 1 does not modify any provision of the base prospectus or the warrant exercise offering prospectus, each of which forms a part of the Registration Statement. Accordingly, such base prospectus and warrant exercise offering prospectus have been omitted from this Amendment No. 1.

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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 AUGUST 12, 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 \$17,488,824 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 \$12,511,176 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 August 10, 2015 was \$0.40 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

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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.

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 vepoloxamer (also known as MST-188), our lead drug 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, heart failure, and stroke. 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 June 30, 2015, we had an accumulated deficit of \$254.9 million. Our cash, cash equivalents, and investment securities were \$43.4 million as of June 30, 2015.

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.

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The Offering

Common stock offered by us:

Shares having an aggregate offering price up to \$12,511,176.

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 7.

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 4.

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

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 annual report on 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 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 \$12,511,176 at an assumed offering price of \$0.40 per share, the last reported sale price of our common stock on the NYSE MKT on August 10, 2015 and after deducting estimated offering commissions and expenses payable by us, our net tangible book value as of June 30, 2015 would have been \$43.1 million, or \$0.22 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 \$0.18 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;

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- the successful completion of our development programs and our ability to manage costs and timelines 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,” “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. 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.

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 June 30, 2015, was approximately \$31.0 million, or approximately \$0.19 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 \$12,511,176 at an assumed offering price of \$0.40 per share, which was the last reported sale price of our common stock on August 10, 2015 on the NYSE MKT, and after deducting estimated commissions and estimated offering expenses, our as-adjusted net tangible book value as of June 30, 2015 would have been approximately \$43.1 million, or approximately \$0.22 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 \$0.18 per share to purchasers of our common stock in this offering, as illustrated by the following table:

Assumed offering price per share	\$0.40
Net tangible book value per share as of June 30, 2015	\$0.19
Increase per share attributable to this offering	\$0.03
As-adjusted net tangible book value per share as of June 30, 2015, after giving effect to this offering	<u>\$0.22</u>
Dilution per share to new investors participating in this offering	<u>\$0.18</u>

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The table above assumes, for illustrative purposes only, an aggregate of 31,277,940 shares of our common stock are sold at a price of \$0.40 per share, for aggregate gross proceeds of \$12,511,176. 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 \$0.40 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$12,511,176 of is sold at that price, would increase the adjusted net tangible book value per share after the offering to \$0.23 per share and increase the dilution in net tangible book value per share to new investors in this offering to \$0.27 per share, after deducting commissions and estimated aggregate offering expenses payable by us. A decrease of \$0.10 per share in the price at which the shares are sold from the assumed offering price of \$0.40 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$12,511,176 is sold at that price, would decrease the adjusted net tangible book value per share after the offering to \$0.21 per share and decrease the dilution in net tangible book value per share to new investors in this offering to \$0.09 per share, after deducting commissions and estimated aggregate offering expenses payable by us. This information is supplied for illustrative purposes only.

The table above is based on 163,614,297 shares of our common stock outstanding as of June 30, 2015 and excludes:

- 13,081,428 shares of our common stock issuable upon exercise of “pre-funded” warrants outstanding as of June 30, 2015, with an exercise price of \$0.01 per share;
- 62,779,804 shares of our common stock issuable upon exercise of warrants outstanding as of June 30, 2015, with a weighted-average exercise price of \$0.83 per share;
- 22,455,269 shares of our common stock issuable upon exercise of options outstanding as of June 30, 2015, with a weighted-average exercise price of \$0.82 per share;
- 22,049,559 shares of our common stock available for future grants under our 2015 Omnibus Incentive Plan as of June 30, 2015; 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 163,614,297 shares were issued and outstanding as of August 10, 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.

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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, 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.

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.

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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;
- 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

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 \$17,488,824 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 \$12,511,176 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.

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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.

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 \$95,000.

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.

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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 (the “Annual Report”), including all material incorporated by reference therein, which includes the portions of our definitive proxy statement on Schedule 14A filed with the SEC on April 29, 2015 incorporated by reference into Part III of the Annual Report;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2015 and June 30, 2015, filed with the SEC on May 11, 2015 and August 12, 2015, respectively;
- 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, March 2, 2015, April 23, 2015, May 19, 2015, May 28, 2015, June 16, 2015, and June 25, 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. 001-32157-04755401).

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 this 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.



Common Stock

PROSPECTUS

Cowen and Company

, 2015

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 \$12,779 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.

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,

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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
 - (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

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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) 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.
- (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.

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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 this Amendment No. 1 to 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 August 12, 2015.

MAST THERAPEUTICS, INC.

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

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.

<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>	August 12, 2015
<u>/s/ Brandi L. Roberts</u> Brandi L. Roberts	Chief Financial Officer and Senior Vice President <i>(Principal Financial and Accounting Officer)</i>	August 12, 2015
<u>*</u> Lewis J. Shuster	Chair of the Board	August 12, 2015
<u>*</u> Howard Dittrich	Director	August 12, 2015
<u>*</u> David A. Ramsay	Director	August 12, 2015

*By /s/ Brandi L. Roberts
Brandi L. Roberts
Attorney-in-Fact

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<u>Exhibit Number</u>	<u>Description</u>	<u>Filed Herewith</u>	<u>Incorporated by Reference</u>		
			<u>Form</u>	<u>File/Film No.</u>	<u>Date Filed</u>
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		Form S-3	333-202960-15722264	03/24/15
4.7	Form of Subordinated Indenture		Form S-3	333-202960-15722264	03/24/15
4.8*	Form of Senior Note				
4.9*	Form of Subordinated Note				
4.10*	Form of Warrant				
4.11*	Form of Unit Agreement				
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		Form S-3	333-202960-15722264	03/24/15
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-3	333-202960-15722264	03/24/15
24.1	Power of attorney (included on the signature page to the registration statement)		Form S-3	333-202960-15722264	03/24/15
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

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 24, 2015 relating to the financial statements, which appears in Mast Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2014. We also consent to the reference to us under the heading "Experts" in such Registration Statement.

/s/ PricewaterhouseCoopers LLP

San Diego, California
August 12, 2015