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FILED PURSUANT TO RULE 424(b)(5)
REGISTRATION NO. 333-206135

PROSPECTUS SUPPLEMENT

(to Prospectus dated October 16, 2015)



\$100,000,000

Common Stock

We have entered into a sales agreement, or Sales Agreement, with Cowen and Company, LLC, or Cowen, dated October 16, 2015, relating to the sale of shares of our common stock offered by this prospectus. In accordance with the terms of the sales agreement, under this prospectus we may offer and sell shares of our common stock, \$0.0001 par value per share, having an aggregate offering price of up to \$100,000,000 from time to time through Cowen, acting as our agent.

Sales of our common stock, if any, under this prospectus will be made by any method permitted that is deemed an "at the market offering" as defined in Rule 415 under the Securities Act of 1933, as amended, or the Securities Act, including sales made directly on or through The NASDAQ Global Market, the existing trading market for our common stock, sales made to or through a market maker other than on an exchange or otherwise, in negotiated transactions at market prices, and/or any other method permitted by law. Cowen is not required to sell any specific amount, but will act as our sales agent using commercially reasonable efforts consistent with its normal trading and sales practices. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

Cowen will be entitled to compensation at a commission rate of up to 3.0% of the gross sales price per share sold under the sales agreement. See "Plan of Distribution" beginning on page S-12 for additional information regarding the compensation to be paid to Cowen. In connection with the sale 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 of Cowen may be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Cowen with respect to certain liabilities, including liabilities under the Securities Act.

Our common stock is listed on The NASDAQ Global Market under the symbol "SNTA." On October 15, 2015, the last reported sale price of our common stock was \$2.04 per share.

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks that we have described on page S-8 of this prospectus under the caption "Risk Factors " and in the documents incorporated by reference in this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

Cowen and Company

The date of this prospectus supplement is October 16, 2015

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Prospectus

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ABOUT THIS PROSPECTUS SUPPLEMENT

You should rely only on the information contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering. We have not, and Cowen has not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and Cowen is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted or in which the person making that offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make an offer or solicitation. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus supplement entitled "Where You Can Find More Information" and "Incorporation of Documents by Reference."

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated October 16, 2015, including the documents incorporated by reference therein, provides more general information, some of which may not apply to this offering. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

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 into the accompanying 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 agreement, 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.

Unless we have indicated otherwise, or the context otherwise requires, references in this prospectus supplement and the accompanying prospectus to "Synta," "the Company," "we," "us" and "our" or similar terms are to Synta Pharmaceuticals Corp. and its subsidiaries.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all of the information that you should consider before deciding to invest in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including the "Risk Factors" section contained in this prospectus supplement, our consolidated financial statements and the related notes thereto and the other documents incorporated by reference in this prospectus supplement and the accompanying prospectus.

Overview

Synta Pharmaceuticals Corp. is an innovative, agile biopharmaceutical company focused on research, development and commercialization of novel oncology medicines that have the potential to change the lives of cancer patients. Our lead oncology drug candidate, ganetespib, a novel heat shock protein 90 (Hsp90) inhibitor, is currently being evaluated in several large randomized clinical trials including GALAXY-2, a pivotal Phase 3 trial in non-small cell lung cancer (NSCLC), as well as in investigator-sponsored trials in breast cancer, ovarian cancer and acute myeloid leukemia (AML). We are also developing several candidates from our proprietary Hsp90 inhibitor Drug Conjugate program (HDC Program), which leverages the preferential accumulation of Hsp90 inhibitors in tumors to selectively deliver a wide array of anti-cancer payloads. Our first clinical candidate from our HDC Program, STA-12-8666, is undergoing testing to enable the filing of an investigational new drug application (IND). Preclinical evaluation of additional HDC candidates is ongoing. We also have an additional clinical-stage oncology candidate: elesclomol, a mitochondrial metabolism inhibitor.

Our Oncology Programs

Ganetespib: Potential Best-in-Class Hsp90 Inhibitor

Preclinical and clinical results have shown that ganetespib is a potent and selective inhibitor of Hsp90, supporting the promise for therapeutic intervention in a broad range of malignancies. Inhibition of Hsp90 by ganetespib leads to the simultaneous degradation of many client proteins and the subsequent death or cell cycle arrest of cancer cells dependent on those proteins. A number of Hsp90 client proteins are also involved in the resistance of cancer cells to other anti-cancer treatments, such as chemotherapy. The ability to reduce cancer-cell drug resistance suggests that the combination of ganetespib with chemotherapies or other anti-cancer agents may result in greater efficacy than those agents administered alone.

We believe that ganetespib has an optimized profile as compared to first generation Hsp90 inhibitors. Some of the key differentiating properties of ganetespib highlighted in results published in *Molecular Cancer Therapeutics* in December 2011 and *Toxicology and Applied Pharmacology* 2012 include:

- ***Novel structure.*** Ganetespib is a small molecule that is structurally unrelated to first-generation, ansamycin class Hsp90 inhibitors, such as 17-AAG or 17-DMAG.
- ***Improved potency.*** In preclinical studies, ganetespib has shown 10-100 times greater potency than 17-AAG across a broad range of cancer cell types as well as activity in animal models that are resistant to treatment with 17-AAG.

- *Absence of molecular component believed to cause liver toxicity.* The hepatotoxicity observed with the ansamycin class of Hsp90 inhibitors is thought to be associated with a chemical moiety (benzoquinone group) not found in the ganetespib clinical structure. In preclinical models, no evidence of changes in liver enzymes or histopathology have been observed.
- *Absence of serious ocular toxicity.* In clinical trials certain Hsp90 inhibitors have caused visual disturbances, suggesting retinal dysfunction. In animal models, ganetespib has not been associated with ocular toxicity. As compared to Hsp90 inhibitors which are known to induce visual symptoms in the clinic and marked retinal photoreceptor death, ganetespib does not appear to elicit photoreceptor injury. Ganetespib has also been shown to have a lower retina/plasma exposure ratio and higher retinal elimination rate than Hsp90 inhibitors which are associated with ocular toxicity.

The differentiating characteristics of ganetespib seen in preclinical and animal studies have also been observed in the human clinical trials we have conducted to date. Specifically, a favorable safety profile has been consistently observed across clinical trials, involving over 1,350 patients treated with ganetespib. Ganetespib has not shown the serious liver or common ocular toxicities reported with other Hsp90 inhibitors, or the neurotoxicity, bone marrow toxicities, and alopecia characteristic of many chemotherapies. Additionally, the most common adverse event reported with ganetespib has been transient, mild or moderate diarrhea, which can be prevented or effectively managed with standard supportive care. Ganetespib has also shown promising activity both in combination with chemotherapy and as a monotherapy, in the clinical trials conducted to date.

GALAXY-2, our most advanced trial for ganetespib, was initiated in early 2013. The GALAXY-2 trial is a global, randomized, multi-center study comparing treatment with docetaxel alone to treatment with ganetespib plus docetaxel in the 2nd-line non-small cell adenocarcinoma patient population, with overall survival, or OS, as the primary endpoint. The GALAXY-2 trial is expected to enroll up to 850 patients. Two event-driven interim analyses of the OS primary endpoint of GALAXY-2 have been pre-specified. The first and second interim analyses will be performed after approximately 60% and 80% of the OS events required for final analysis have occurred, respectively.

Based on current projections and statistical assumptions, we expect that the first GALAXY-2 interim OS analysis will be conducted by the end of 2015 and that the second interim OS analysis and the final OS analysis will be conducted in 2016. Assuming positive interim results from the ongoing GALAXY-2 trial of ganetespib and pending regulatory feedback, we plan to seek regulatory approval of ganetespib for NSCLC in 2016.

In addition to the GALAXY-2 trial, ganetespib is currently being studied in a number of randomized, investigator-sponsored clinical trials, including a Phase 3 clinical trial for acute myeloid leukemia (AML), and Phase 2 clinical trials for ovarian and breast cancer.

Hsp90 inhibitor Drug Conjugate (HDC) Program

In September 2013, we announced the launch of a novel, proprietary small molecule cancer drug development program: the HDC Program. This innovative approach to tumor targeted delivery is being developed to capitalize on the prolonged retention of Hsp90 inhibitors in tumors to trap an active agent of interest inside cancer cells. The HDC Program builds on our extensive expertise in the science of Hsp90.

The HDC platform is based on the observation that small molecule inhibitors of Hsp90 are retained in tumors for as much as 20 times longer than in blood or normal tissue. Preclinical experiments have shown that following intravenous administration in animals, ganetespib can persist in tumor cells for over a week, while it is cleared from blood and normal tissues in a matter of hours. Similar results demonstrating this characteristic have been published by others using first-generation Hsp90 inhibitors such as 17-AAG and its derivatives, as well as other classes of Hsp90 inhibitors. This property of the Hsp90 inhibitor class is believed to be due to overexpression of an active form of Hsp90 in cancer cells that preferentially binds Hsp90 inhibitors, as compared to normal tissues. Even weak Hsp90 inhibitors that do not engage degradation of Hsp90 client proteins can be retained for days by cancer cells, potentially enabling use of this property purely as a targeting mechanism to deliver an anticancer drug into cancer cells.

Most cancer drugs are given systemically and therefore can affect normal tissues and organs and cause toxicity. In recognition of this problem, several therapeutic strategies have been developed to attempt selective delivery of anticancer drugs to tumors. For example, Antibody-Drug Conjugates (ADCs) are used for the delivery of potent anti-cancer payloads to tumors. Conceptually, HDCs are designed for targeted drug delivery with potentially broader applicability relative to ADCs. Because of its unique properties, we believe that Hsp90 may represent one of the most compelling targets for delivering drug payloads to tumors. HDCs are drug candidates consisting of an Hsp90 inhibitor (targeting moiety) joined to an anti-cancer agent (payload) via a cleavable chemical linker optimized for controlled release of payload drug inside cancer cells. HDCs are small molecules that do not require cell surface antigens for targeting or active transport (endocytosis) for cellular uptake. Upon cell entry typically via passive diffusion, HDCs can bind to intracellular Hsp90 that is present in significant amounts in a wide range of cancers.

Upon systemic administration, HDCs have the potential to achieve significantly higher concentrations of active anticancer drugs (payloads) in tumors than the concentrations achieved when such anticancer drugs are given in their original, unconjugated form. It is important to note that such high concentrations are sustained over prolonged periods of time, thus significantly increasing the exposure of tumors to the anticancer drug relative to the exposure that can be achieved when such anticancer drugs are given in their original, unconjugated form.

We believe that our HDC platform has the potential to enable the rapid creation of an extensive proprietary pipeline of novel anticancer drugs that we may elect to develop independently or co-develop with selected partners. We have developed Hsp90 inhibitor conjugated chemotherapeutics, kinase inhibitors, hormone therapies, immunomodulators, and epigenetic modifiers, creating the potential for next-generation compounds in each of these categories. Examples include Hsp90 inhibitor-conjugated bendamustine, temozolomide, doxorubicin, 5-FU, pemetrexed, gemcitabine, SN-38, topotecan, vorinostat, panobinostat, fulvestrant, abiraterone, lenalidomide, pomalidomide, docetaxel, carboplatin, bortezomib, carfilzomib, flavopiridol, staurosporine, vemurafenib, sunitinib, and sorafenib.

In the first quarter of 2015, we advanced STA-12-8666, a conjugate of an Hsp90 inhibitor and SN-38, the highly potent active metabolite of the widely used drug irinotecan, into IND enabling studies. We expect to submit an IND for STA-12-8666 by the first quarter of 2016. Preclinical pharmacological studies have shown that SN-38 exposure in tumors (concentration over time) is significantly greater with STA-12-8666 compared to irinotecan. Activity of STA-12-8666 has been evaluated preclinically in more than a dozen tumor models. Results from these studies show consistently higher activity than irinotecan at the equivalent doses and respective maximum tolerated doses (MTDs). Preclinical and animal toxicity studies conducted to date also suggest an improved

tolerability profile for STA-12-8666 as compared to irinotecan. In addition to STA-12-8666, we expect to identify one additional HDC drug candidate to nominate for preclinical development in the first half of 2016 and hope to initiate IND-enabling studies in 2016.

Elesclomol (Mitochondria-Targeting Agent)

Elesclomol is a first-in-class investigational drug candidate that triggers programmed cell death (apoptosis) in cancer cells through a novel mechanism: disrupting cancer cell energy metabolism. Preclinical experiments and findings in three randomized clinical trials have shown that lactate dehydrogenase (LDH), a key enzyme in cellular energy metabolism, is an important predictor of elesclomol treatment outcome.

We are evaluating the use of elesclomol in combination with paclitaxel in ovarian cancer. In March 2011, the Gynecological Oncology Group (GOG) initiated a Phase 2 clinical trial of elesclomol in combination with paclitaxel for the treatment of persistent or recurrent ovarian, fallopian tube or primary peritoneal cancer for patients with total baseline serum LDH level less than 0.8 times the upper limit of normal (ULN). The GOG is a non-profit organization with the purpose of promoting excellence in the quality and integrity of clinical and basic scientific research in the field of gynecologic malignancies. The National Cancer Institute is providing financial support of up to approximately \$300,000 for the trial through its Cancer Therapy Evaluation Program. The ovarian cancer trial met the pre-specified efficacy requirement to advance to stage 2, indicating potential activity in this difficult-to-treat patient population with limited treatment options. Enrollment of stage 2 of this study has been completed.

Our Drug Candidate Pipeline

The following table summarizes the key ongoing trials and current development status for ganetespib and our HDC program:



Our Strategy

We are committed to research, development and commercialization of novel oncology medicines that change cancer patients' lives. In February 2015, we outlined a new corporate strategy aimed at focusing our resources on achieving key value creating milestones in 2015 and 2016. Important elements of our strategy include:

Maximizing the value of our lead development program, ganetespi

- *Develop and seek approval for ganetespi in North America and Europe.* Assuming positive interim results from our ongoing GALAXY-2 trial of ganetespi and pending regulatory feedback, we plan to submit a New Drug Application (NDA) for ganetespi for use in NSCLC in 2016. We also plan to seek regulatory approval in Europe on the same timeframe. Pending positive data from clinical trials with ganetespi in other indications and pending regulatory feedback, we plan to seek regulatory approval or initiate registration trials in such indications.
- *Commercialize ganetespi.* We currently have global development, marketing and commercialization rights for ganetespi. If approved, we intend to commercialize ganetespi in the United States and, at the appropriate time, enter into collaborations for further development, marketing and commercialization of ganetespi in particular geographies outside the United States.
- *Expand ganetespi development program.* We expect to expand the breadth of the ganetespi development program to include multiple potential registration paths and combination regimens.
- *Pursue a biomarker strategy to further optimize ganetespi potential.* We intend to identify the patient populations most likely to derive benefit from treatment with ganetespi and we anticipate using these findings to optimize future ganetespi clinical development.

Advancing candidates from our HDC Program into the clinic

- *Pursue internal development of select candidates.* We expect to submit an IND for our lead HDC candidate, STA-12-8666, by the first quarter of 2016, and nominate one additional HDC candidate for IND enabling studies in the first half of 2016.
- *Pursue strategic partnerships for our HDC Program.* We plan on exploring potential strategic partnerships for our HDC Program to take advantage of a broader set of opportunities than we could exploit alone, while continuing to increase the scope and breadth of our intellectual property.

Optimizing our drug candidate pipeline and research plans

- *Complement our development portfolio through external partnerships and business development activities.* We will evaluate the merit and fit of in-licensing, co-developing or acquiring new drug candidates and technologies that either support ongoing development efforts with existing candidates or add breadth to our portfolio.
- *Focus internal research plans on key programs.* We are focusing our research efforts solely on *generating* promising new HDC drug candidates with selected payloads that have broad therapeutic potential and that will lead to further expanding our ganetespi biomarker research effort.

Optimizing the Company's operating model

- *Focus on operational efficiency.* We intend to focus strongly on managing our resources efficiently and strengthening our cash position, such that we have multiple options for continuing to advance our drug candidates either on our own or through partnerships.

Company History and Available Information

We commenced operations in July 2001. In September 2002, we acquired Principia Associates, Inc., which had previously acquired Shionogi BioResearch Corp., a U.S.-based drug discovery subsidiary of the Japanese pharmaceutical company, Shionogi & Co., Ltd. In this acquisition, we acquired a unique chemical compound library, an integrated set of drug discovery capabilities, and a pipeline of preclinical and research programs. Since 2002, we have been advancing these programs into later stages of development, discovering and developing additional drug candidates and expanding our management and scientific teams and capabilities to support more advanced stages of drug development and commercialization.

Our principal executive offices are located at 45 Hartwell Avenue, Lexington, Massachusetts 02421, and our telephone number is (781) 274-8200. Our website address is www.syntapharma.com. The information contained on our website is not incorporated by reference into, and does not form any part of, this prospectus supplement or the accompanying prospectus. We have included our website address as a factual reference and do not intend it to be an active link to our website. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and all amendments to those reports, are available free of charge through the "Investors—SEC Filings" section of our website as soon as reasonably practicable after such materials have been electronically filed with, or furnished to, the SEC.

Our trademarks include, without limitation, Synta Pharmaceuticals, our corporate logo and the GALAXY Trial. Other service marks, trademarks and trade names contained in this prospectus supplement, the accompanying prospectus or the documents incorporated by reference herein and therein are the property of their respective owners.

The Offering

Common stock offered by us	Shares of our common stock having an aggregate offering price of up to \$100 million.
Manner of offering	"At the market offering" that may be made from time to time on The NASDAQ Global Market or other market for our common stock in the U.S. through our agent, Cowen. See the section entitled "Plan of Distribution" below.
Use of proceeds	We intend to use the net proceeds of this offering for our operations, including, but not limited to, general corporate purposes, which may include research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, acquisitions of new technologies, capital expenditures and working capital. See the section entitled "Use of Proceeds" below.
Risk factors	You should read the "Risk Factors" section of this prospectus supplement, in the accompanying prospectus and in the documents incorporated by reference in this prospectus supplement for a discussion of factors to consider before deciding to purchase shares of our common stock.
NASDAQ Global Market symbol	SNTA

RISK FACTORS

Investment in our common stock involves risks. Before deciding whether to invest in our common stock, you should consider carefully the risk factors discussed below and those contained in the section entitled "Risk Factors" contained in our Annual Report on Form 10-K for the fiscal year ended December 31, 2014, as filed with the Securities and Exchange Commission, or the SEC, on March 12, 2015, which is incorporated herein by reference in its entirety, as well as any amendment or update to our risk factors reflected in subsequent filings with the SEC. If any of the risks or uncertainties described in our SEC filings actually occurs, our business, financial condition, results of operations or cash flow could be materially and adversely affected. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. The risks and uncertainties we have described are not the only ones facing our company. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business operations.

Risks Related to This Offering

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.

Our management will have broad discretion as to the use of the net proceeds from any offering by us and could use them for purposes other than those contemplated at the time 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 the proceeds will be invested in a way that does not yield a favorable, or any, return for Synta.

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

The offering price per share in this offering may exceed the pro forma net tangible book value per share of our common stock outstanding prior to this offering. Assuming that an aggregate of 49,019,607 shares of our common stock are sold at a price of \$2.04 per share, the last reported sale price of our common stock on The NASDAQ Global Market on October 15, 2015 for aggregate gross proceeds of approximately \$100 million, and after deducting commissions and estimated aggregate offering expenses payable by us, you will experience immediate dilution of \$1.10 per share, representing the difference between the assumed offering price of \$2.04 per share and our pro forma as adjusted net tangible book value per share as of June 30, 2015 after giving effect to this offering at the assumed size and offering price. The exercise of outstanding stock options will result in further dilution of your investment. See the section below entitled "Dilution" for a more detailed illustration of the dilution you would incur if you participate in this offering.

Sales of a significant number of shares of our common stock in the public markets, or the perception that such sales could occur, could depress the market price of our common stock.

Sales of a substantial number of shares of our common stock in the public markets could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities. We cannot predict the effect that future sales of our common stock would have on the market price of our common stock.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering contain "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

- the safety and efficacy of our product candidates;
- the timing, development and progress of our clinical and preclinical programs (including the timing of results of our ongoing trials and initiation of additional trials for ganetespib);
- our estimated expenditures and projected cash needs, including the sufficiency of cash resources to fund operations; and
- the use of proceeds from this offering.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "potential" and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading "Risk Factors" of this prospectus supplement and in our SEC filings. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement.

You should read this prospectus supplement, the accompanying prospectus, the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

USE OF PROCEEDS

The amount of proceeds from this offering will depend upon the number of shares of our common stock sold and the market price at which they are sold. There can be no assurance that we will be able to sell any shares under or fully utilize the sales agreement with Cowen as a source of financing. We intend to use the net proceeds from this offering for general corporate purposes, which may include research and development expenditures, clinical trial expenditures, manufacture

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and supply of drug substance and drug products, acquisitions of new technologies, capital expenditures and working capital.

We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds from this offering. We have no current plans, commitments or agreements with respect to any acquisitions and may not make any acquisitions. Pending application of the net proceeds as described above, we intend to invest the net proceeds of the offering in short-term, investment-grade, interest-bearing securities.

DILUTION

If you purchase our common stock in this offering, your interest will be diluted to the extent of the difference between the public offering price per share and the pro forma as adjusted net tangible book value per share of our common stock after this offering. We calculate pro forma net tangible book value per share by subtracting our total liabilities from our total tangible assets and dividing the difference by the number of outstanding shares of our common stock as of June 30, 2015, after giving pro forma effect to the sale, after June 30, 2015, of 3,614,511 shares of our common stock pursuant to a previous at the market issuance sales agreement, dated July 18, 2014, with MLV & Co., LLC for aggregate net proceeds of approximately \$7.7 million.

Our pro forma net tangible book value at June 30, 2015 was \$76.7 million, or \$0.56 per share. After giving effect to the sale of our common stock in this offering in the aggregate amount of \$100 million at an assumed offering price of \$2.04 per share, the last reported sale price of our common stock on The NASDAQ Global Market on October 15, 2015, and after deducting estimated offering commissions and expenses payable by us, our pro forma as adjusted net tangible book value as of June 30, 2015 would have been \$174.6 million, or \$0.94 per share of common stock. This represents an immediate increase in the pro forma net tangible book value per share of \$0.38 to our existing stockholders and an immediate dilution of \$1.10 per share to new investors. The following table illustrates this per share dilution:

Assumed public offering price per share	\$ 2.04
Pro forma net tangible book value per share as of June 30, 2015	0.56
Increase per share attributable to this offering	0.38
Pro forma as adjusted net tangible book value per share after this offering	0.94
Dilution per share to new investors	\$ 1.10

The table above assumes for illustrative purposes that an aggregate of 49,019,607 shares of our common stock are sold at a price of \$2.04 per share, the last reported sale price of our common stock on The NASDAQ Global Market on October 15, 2015, for aggregate gross proceeds of approximately \$100 million. The shares sold in this offering, if any, 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 \$2.04 per share shown in the table above to \$2.14 per share, assuming 46,728,971 shares of our common stock in the aggregate amount of \$100 million is sold at that price, would result in dilution to new investors in this offering of \$1.19 per share, after deducting commissions and estimated 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 \$2.04 per share shown in the table above to \$1.94 per share, assuming 51,546,391 shares of our common stock in the aggregate amount of \$100 million is sold at that price, would result in dilution to new investors in this offering of

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\$1.02 per share, after deducting commissions and estimated offering expenses payable by us. This information is supplied for illustrative purposes only.

The information above does not include:

- 9,565,682 shares of our common stock issuable upon exercise of stock options outstanding as of June 30, 2015 under our stock option plans as of that date, at a weighted average exercise price of \$5.32 per share; and
- 8,740,968 shares of our common stock available as of June 30, 2015 for future grant or issuance pursuant to our stock-based plan for employees, directors and consultants.

To the extent that options outstanding as of June 30, 2015 have been or are exercised, or other shares are issued, investors purchasing shares in this offering could experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

DIVIDEND POLICY

We have never paid or declared any cash dividends on our common stock and we are currently prohibited from making any dividend payment under the terms of our loan and security agreement with General Electric Capital Corporation and MidCap Funding III, LLC. We currently intend to retain all available funds and any future earnings to fund the development and expansion of our business, and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our board of directors and will depend on our financial condition, results of operations, contractual restrictions, capital requirements, and other factors that our board of directors deems relevant.

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Cowen, under which we may issue and sell from time to time up to \$100,000,000 of our common stock through Cowen as our sales agent. Sales of our common stock, if any, will be made at market prices by any method that is deemed to be an "at the market offering" as defined in Rule 415 under the Securities Act, including sales made directly on The Nasdaq Global Market or any other trading market for our common stock, or sales to or through a market maker other than on an exchange. If authorized by us in writing, Cowen may also sell our shares of common stock by any other method permitted by law, including negotiated transactions, and Cowen may also purchase shares of our common stock as principal.

Cowen will offer our 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. Cowen or we may suspend the offering of our common stock being made through Cowen under the sales agreement upon proper notice to the other party. Cowen and we 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 equals up to 3.0% of the gross sales price of the shares sold through it pursuant to the sales agreement. We have also agreed to reimburse Cowen up to \$50,000 of Cowen's actual outside legal expenses incurred by Cowen in connection with this offering, inclusive of any fees associated with a FINRA review. We estimate that the total expenses of the offering payable by us, excluding commissions payable to Cowen under the sales agreement, will be approximately \$60,000.

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 Nasdaq Global Market on 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 volume weighted average price of the shares sold, the percentage of the daily trading volume and the net proceeds to us.

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.

To the extent required by Regulation M, Cowen will not engage in any market making activities involving our common stock while the offering is ongoing under this prospectus.

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

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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 our 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. As sales agent, Cowen will not engage in any transactions that stabilizes our common stock.

Our common stock is listed on The Nasdaq Global Market and trades under the symbol "SNTA." The transfer agent of our common stock is Computershare Trust Company, N.A.

Cowen and/or its affiliates have provided, and may in the future provide, various investment banking and other financial services for us for which services they have received and, may in the future receive, customary fees.

LEGAL MATTERS

The validity of the shares of common stock offered hereby will be passed upon for us by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts. LeClairRyan, A Professional Corporation, New York, New York, is counsel for Cowen in connection with this offering.

EXPERTS

The consolidated financial statements of Synta Pharmaceuticals Corp. appearing in its Annual Report (Form 10-K) for the year ended December 31, 2014, and the effectiveness of Synta Pharmaceuticals Corp.'s internal control over financial reporting as of December 31, 2014, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their reports thereon, included therein, and incorporated herein by reference. Such consolidated financial statements are incorporated herein by reference in reliance upon such reports given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference facilities at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference facilities. SEC filings are also available at the SEC's website at <http://www.sec.gov>.

This prospectus supplement and the accompanying prospectus are only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act of 1933, as amended, and therefore omits certain information contained in the registration statement. We have also filed exhibits and schedules with the registration statement that are excluded from this prospectus supplement, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document. You may inspect a copy of the registration statement, including the exhibits and schedules, without charge, at the public reference room or obtain a copy from the SEC upon payment of the fees prescribed by the SEC.

We also maintain a website at www.syntapharma.com, through which you can access our SEC filings. The information set forth on our website is not part of this prospectus supplement.

INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" information from other documents that we file with them, which means that we can disclose important information in this prospectus supplement by referring to those documents. The information incorporated by reference is considered to be part of this prospectus supplement, and information that we file later with the SEC will automatically update and supersede the information in this prospectus supplement. We incorporate by reference the following documents (unless otherwise noted, the SEC file number for each of the documents listed below is 001-33277):

- our Annual Report on Form 10-K, for the fiscal year ended December 31, 2014, filed with the SEC on March 12, 2015;
- our Quarterly Reports on Form 10-Q, for the quarter ended March 31, 2015 and June 30, 2015, filed with the SEC on May 7, 2015 and August 6, 2015, respectively;
- our Current Reports on Form 8-K filed on February 5, 2015, March 6, 2015, April 1, 2015, April 6, 2015, April 27, 2015 and June 15, 2015;
- the portions of our Definitive Proxy Statement on Schedule 14A that are deemed "filed" with the SEC under the Securities Exchange Act of 1934, as amended, filed on April 30, 2015;
- the description of our common stock contained in our Registration Statement on Form 8-A filed on January 26, 2007, including any amendment or report filed for the purpose of updating such description; and
- all reports and other documents subsequently filed by us pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Securities Exchange Act of 1934, as amended, after the date of this prospectus supplement and prior to the termination of this offering shall be deemed to be incorporated by reference in this prospectus supplement and to be a part hereof from the date of filing such reports and other documents.

You may request, orally or in writing, a copy of any or all of the documents incorporated herein by reference. These documents will be provided to you at no cost, by contacting: Investor Relations, Synta Pharmaceuticals Corp., 45 Hartwell Avenue, Lexington, MA 02421, (781) 274-8200.

PROSPECTUS

SYNTA PHARMACEUTICALS CORP.

**\$300,000,000
COMMON STOCK
PREFERRED STOCK
DEBT SECURITIES
WARRANTS
RIGHTS
PURCHASE CONTRACTS
UNITS**

This prospectus will allow us to issue, from time to time at prices and on terms to be determined at or prior to the time of the offering, up to \$300,000,000 of any combination of the securities described in this prospectus, either individually or in units. We may also offer common stock or preferred stock upon conversion of or exchange for the debt securities; common stock upon conversion of or exchange for the preferred stock; common stock, preferred stock or debt securities upon the exercise of warrants, rights or performance of purchase contracts; or any combination of these securities upon the performance of purchase contracts.

This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide you with the specific terms of any offering in one or more supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any prospectus supplement, as well as any documents incorporated by reference into this prospectus or any prospectus supplement, carefully before you invest.

Our securities may be sold directly by us to you, through agents designated from time to time or to or through underwriters or dealers. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus and in the applicable prospectus supplement. If any underwriters or agents are involved in the sale of our securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, commissions or discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Our common stock is listed on The NASDAQ Global Market under the symbol "SNTA." On October 15, 2015, the last reported sale price of our common stock was \$2.04 per share. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The NASDAQ Global Market or any securities market or other securities exchange of the securities covered by the prospectus supplement. Prospective purchasers of our securities are urged to obtain current information as to the market prices of our securities, where applicable.

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks that we have described on page 3 of this prospectus under the caption "Risk Factors." We may include specific risk factors in supplements to this prospectus under the caption "Risk Factors." This prospectus may not be used to sell our securities unless accompanied by a prospectus supplement.

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

The date of this prospectus is October 16, 2015.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a "shelf" registration process. Under this shelf registration process, we may offer shares of our common stock and preferred stock, various series of debt securities and/or warrants, rights or purchase contracts to purchase any of such securities, either individually or in units, in one or more offerings, with a total value of up to \$300,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained or incorporated by reference in this prospectus. However, no prospectus supplement will offer a security that is not registered and described in this prospectus at the time of its effectiveness. This prospectus, together with the applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to the offering of securities under this prospectus. You should carefully read this prospectus, the applicable prospectus supplement, the information and documents incorporated herein by reference and the additional information under the heading "Where You Can Find More Information" before making an investment decision.

You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security.

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 the accompanying 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.

This prospectus may not be used to consummate sales of our securities, unless it is accompanied by a prospectus supplement. To the extent there are inconsistencies between any prospectus supplement, this prospectus and any documents incorporated by reference, the document with the most recent date will control.

Unless the context otherwise requires, "Synta," "the Company," "we," "us," "our" and similar terms refer to Synta Pharmaceuticals Corp. and our subsidiaries.

Our trademarks include, without limitation, Synta Pharmaceuticals, our corporate logo and the GALAXY trial. Other service marks, trademarks and trade names contained in this prospectus supplement, the accompanying prospectus or the documents incorporated by reference herein and therein are the property of their respective owners.

PROSPECTUS SUMMARY

The following is a summary of what we believe to be the most important aspects of our business and the offering of our securities under this prospectus. We urge you to read this entire prospectus, including the more detailed consolidated financial statements, notes to the consolidated financial statements and other information incorporated by reference from our other filings with the SEC or included in any applicable prospectus supplement. Investing in our securities involves risks. Therefore, carefully consider the risk factors set forth in any prospectus supplements and in our most recent annual and quarterly filings with the SEC, as well as other information in this prospectus and any prospectus supplements and the documents incorporated by reference herein or therein, before purchasing 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.

About Synta Pharmaceuticals Corp.

We are an innovative, agile biopharmaceutical company focused on research, development and commercialization of novel oncology medicines that have the potential to change the lives of cancer patients. Our lead oncology drug candidate, ganetespib, a novel heat shock protein 90 (Hsp90) inhibitor, is currently being evaluated in several large randomized clinical trials including GALAXY-2, a pivotal Phase 3 trial in non-small cell lung cancer (NSCLC), as well as breast cancer, ovarian cancer and acute myeloid leukemia (AML). We are also evaluating several candidates from our proprietary Hsp90 inhibitor Drug Conjugate program (HDC Program), which leverages the preferential accumulation of Hsp90 inhibitors in tumors to selectively deliver a wide array of anti-cancer payloads. Our first clinical candidate from our HDC Program, STA-12-8666, is undergoing testing to enable the filing of an investigational new drug application (IND). Preclinical evaluation of additional HDC candidates is ongoing. We also have an additional clinical-stage oncology candidate: elesclomol, a mitochondrial metabolism inhibitor.

We believe that the broad clinical and commercial potential of our drug candidates, together with our operational capabilities and additional competitive advantages, provide us with multiple, sustainable growth opportunities. Our capabilities and advantages include: our intellectual property portfolio; the full ownership of all commercial rights in all geographic regions to our programs; our ability to integrate discovery, translational, and clinical research to optimize our development programs and further strengthen our intellectual property position; our operational experience in effectively managing large-scale, global clinical programs; our strong network of relationships with leading investigators and medical centers; our proprietary chemical compound library and the strength of our drug discovery platform; and the skills, talent, and degree of industry experience of our employees.

Additional Information

We commenced operations in July 2001. In September 2002, we acquired Principia Associates, Inc., which had previously acquired Shionogi BioResearch Corp., a U.S.-based drug discovery subsidiary of the Japanese pharmaceutical company, Shionogi & Co., Ltd. In this acquisition, we acquired a unique chemical compound library, an integrated set of drug discovery capabilities, and a pipeline of preclinical and research programs. Since 2002, we have been advancing these programs into later stages of development, discovering and developing additional drug candidates and expanding our management and scientific teams and capabilities to support more advanced stages of drug development and commercialization.

Our principal executive offices are located at 45 Hartwell Avenue, Lexington, Massachusetts 02421, and our telephone number is (781) 274-8200. Our website address is www.syntapharma.com. The information contained on our website is not incorporated by reference into, and does not form any part of, this prospectus. We have included our website address as a factual reference and do not intend it to

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be an active link to our website. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and all amendments to those reports, are available free of charge through the "Investors—SEC Filings" section of our website as soon as reasonably practicable after such materials have been electronically filed with, or furnished to, the SEC.

Offerings Under This Prospectus

Under this prospectus, we may offer shares of our common stock and preferred stock, various series of debt securities and/or warrants, rights or purchase contracts to purchase any of such securities, either individually or in units, with a total value of up to \$300,000,000, from time to time at prices and on terms to be determined by market conditions at the time of the offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity, if applicable;
- rates and times of payment of interest or dividends, if any;
- redemption, conversion or sinking fund terms, if any;
- voting or other rights, if any; and
- conversion or exercise prices, if any.

The prospectus supplement also may add, update or change information contained in this prospectus or in documents we have incorporated by reference into this prospectus. However, no prospectus supplement will offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We may sell the securities directly to investors or to or through agents, underwriters or dealers. We, and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of securities. If we offer securities through agents or underwriters, we will include in the applicable prospectus supplement:

- the names of those agents or underwriters;
- applicable fees, discounts and commissions to be paid to them;
- details regarding over-allotment options, if any; and
- the net proceeds to us.

This prospectus may not be used to consummate a sale of any securities unless it is accompanied by a prospectus supplement.

RISK FACTORS

Investing in our securities involves significant risk. The prospectus supplement applicable to each offering of our securities may contain a discussion of the risks applicable to an investment in Synta. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading "Risk Factors" in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under the heading "Risk Factors" included in our most recent

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annual report on Form 10-K, as revised or supplemented by our subsequent quarterly reports on Form 10-Q or our current reports on Form 8-K on file with the SEC, all of which are incorporated herein by reference, and which may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations.

RATIO OF EARNINGS TO FIXED CHARGES

Any time debt securities are offered pursuant to this prospectus, we will provide a table setting forth our ratio of earnings to fixed charges on a historical basis in the applicable prospectus supplement, if required.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

The SEC encourages companies to disclose forward-looking information so that investors can better understand a company's future prospects and make informed investment decisions. This prospectus and the documents we have filed with the SEC that are incorporated herein by reference contain such "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995.

Such statements in connection with any discussion of future operations or financial performance are identified by the use of words such as "may," "anticipate," "estimate," "expect," "project," "intend," "plan," "believe," and other words and terms of similar meaning. Such statements are based on management's expectations and are subject to certain factors, risks and uncertainties that may cause actual results, outcome of events, timing and performance to differ materially from those expressed or implied by such statements. These risks and uncertainties include, but are not limited to, the risk that we may be unable to develop and achieve commercial success for our drug candidates; the risk that we may be unable to discover drugs that are safer and more efficacious than our competitors; the risk that we may be unable to establish and maintain manufacturing arrangements for our products; the possibility of delays in the research and development necessary to select drug development candidates and delays in clinical trials; the risk that clinical trials may not result in marketable products; the risk that we may be unable to successfully finance and secure regulatory approval of and market our drug candidates, or that clinical trials will not be completed on the timelines we have estimated; uncertainties about our ability to obtain new corporate collaborations and acquire new technologies on satisfactory terms, if at all; the development of competing products; the risk that we may be unable to protect our proprietary technologies; the risk of patent-infringement claims; risks of new, changing and competitive technologies and regulations in the United States and internationally; and other factors detailed under the heading "Risk Factors" in this prospectus as updated and supplemented by the discussion of risks and uncertainties under "Risk Factors" contained in any supplements to this prospectus and in our most recent annual report on Form 10-K, as revised or supplemented by our subsequent quarterly reports on Form 10-Q or our current reports on Form 8-K, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference. The information contained in this document is believed to be current as of the date of this document. We do not intend to update any of the forward-looking statements after the date of this document to conform these statements to actual results or to changes in our expectations, except as required by law.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in this prospectus or in any document incorporated herein by reference might not occur. Investors are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this prospectus or the date of the document incorporated by reference in this prospectus. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new

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information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

USE OF PROCEEDS

We cannot assure you that we will receive any proceeds in connection with securities which may be offered pursuant to this prospectus. Unless otherwise indicated in the applicable prospectus supplement, we intend to use any net proceeds from the sale of securities under this prospectus for our operations and for other general corporate purposes, including, but not limited to, repayment or refinancing of existing indebtedness or other corporate borrowings, working capital, intellectual property protection and enforcement, capital expenditures, investments, acquisitions or collaborations, repurchases and redemption of our securities, research and development and product development. We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds, if any, we receive in connection with securities offered pursuant to this prospectus for any purpose. Pending application of the net proceeds as described above, we may initially invest the net proceeds in short-term, investment-grade, interest-bearing securities or apply them to the reduction of short-term indebtedness.

PLAN OF DISTRIBUTION

We may offer securities under this prospectus from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities (1) through underwriters or dealers, (2) through agents or (3) directly to one or more purchasers, or through a combination of such methods. We may distribute the securities from time to time in one or more transactions at:

- a fixed price or prices, which may be changed from time to time;
- market prices prevailing at the time of sale;
- prices related to the prevailing market prices; or
- negotiated prices.

We may directly solicit offers to purchase the securities being offered by this prospectus. We may also designate agents to solicit offers to purchase the securities from time to time. We will name in a prospectus supplement any underwriter or agent involved in the offer or sale of the securities.

If we utilize a dealer in the sale of the securities being offered by this prospectus, we will sell the securities to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

If we utilize an underwriter in the sale of the securities being offered by this prospectus, we will execute an underwriting agreement with the underwriter at the time of sale, and we will provide the name of any underwriter in the prospectus supplement which the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we, or the purchasers of the securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and the underwriter may compensate those dealers in the form of discounts, concessions or commissions.

With respect to underwritten public offerings, negotiated transactions and block trades, we will provide in the applicable prospectus supplement information regarding any compensation we pay to underwriters, dealers or agents in connection with the offering of the securities, and any discounts,

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concessions or commissions allowed by underwriters to participating dealers. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act of 1933, as amended, or the Securities Act, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Shares of our common stock sold pursuant to the registration statement of which this prospectus is a part will be authorized for quotation and trading on The NASDAQ Global Market. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The NASDAQ Global Market or any securities market or other securities exchange of the securities covered by the prospectus supplement. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

In order to facilitate the offering of the securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing the applicable security in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if the securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

In compliance with the guidelines of the Financial Industry Regulatory Authority, Inc., or FINRA, the maximum consideration or discount to be received by any FINRA member or independent broker dealer may not exceed 8% of the aggregate amount of the securities offered pursuant to this prospectus and any applicable prospectus supplement.

The underwriters, dealers and agents may engage in other transactions with us, or perform other services for us, in the ordinary course of their business.

DESCRIPTION OF COMMON STOCK

We are authorized to issue 200,000,000 shares of common stock, par value \$0.0001 per share. On August 3, 2015, we had 136,442,378 shares of common stock outstanding and approximately 50 stockholders of record.

The following summary of certain provisions of our common stock does not purport to be complete. You should refer to our restated certificate of incorporation and our restated bylaws, both of which are included as exhibits to the registration statement of which this prospectus is a part. The summary below is also qualified by provisions of applicable law.

General

Holders of common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders, and do not have cumulative voting rights. Subject to preferences that may be applicable to any outstanding shares of preferred stock, holders of common stock are entitled to receive ratably such dividends, if any, as may be declared from time to time by our board of directors out of funds legally available for dividend payments. All shares of common stock outstanding as of the date of this prospectus and, upon issuance and sale, all shares of common stock that we may offer pursuant to this prospectus, will be fully paid and nonassessable. The holders of common stock have no preferences or rights of conversion, exchange, pre-emption or other subscription rights. There are no redemption or sinking fund provisions applicable to the common stock. In the event of any liquidation, dissolution or winding-up of our affairs, holders of common stock will be entitled to share ratably in our assets that are remaining after payment or provision for payment of all of our debts and obligations and after liquidation payments to holders of outstanding shares of preferred stock, if any.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

NASDAQ Global Market

Our common stock is listed for quotation on The NASDAQ Global Market under the symbol "SNTA."

DESCRIPTION OF PREFERRED STOCK

We are authorized to issue 5,000,000 shares of preferred stock, par value \$0.0001 per share. As of August 3, 2015, no shares of our preferred stock were outstanding or designated. The following summary of certain provisions of our preferred stock does not purport to be complete. You should refer to our restated certificate of incorporation and our restated bylaws, both of which are included as exhibits to the registration statement of which this prospectus is a part. The summary below is also qualified by provisions of applicable law.

General

Our board of directors may, without further action by our stockholders, from time to time, direct the issuance of shares of preferred stock in series and may, at the time of issuance, determine the rights, preferences and limitations of each series, including voting rights, dividend rights and redemption and liquidation preferences. Satisfaction of any dividend preferences of outstanding shares of preferred stock would reduce the amount of funds available for the payment of dividends on shares of our common stock. Holders of shares of preferred stock may be entitled to receive a preference payment in the event of any liquidation, dissolution or winding-up of our company before any payment

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is made to the holders of shares of our common stock. In some circumstances, the issuance of shares of preferred stock may render more difficult or tend to discourage a merger, tender offer or proxy contest, the assumption of control by a holder of a large block of our securities or the removal of incumbent management. Upon the affirmative vote of our board of directors, without stockholder approval, we may issue shares of preferred stock with voting and conversion rights which could adversely affect the holders of shares of our common stock.

If we offer a specific series of preferred stock under this prospectus, we will describe the terms of the preferred stock in the prospectus supplement for such offering and will file a copy of the certificate establishing the terms of the preferred stock with the SEC. To the extent required, this description will include:

- the title and stated value;
- the number of shares offered, the liquidation preference, if any, per share and the purchase price;
- the dividend rate(s), period(s) and/or payment date(s), or method(s) of calculation for such dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption, if applicable;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price (or how it will be calculated) and conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price (or how it will be calculated) and exchange period;
- voting rights, if any, of the preferred stock;
- a discussion of any material and/or special U.S. federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the affairs of Synta; and
- any material limitations on issuance of any class or series of preferred stock ranking pari passu with or senior to the series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of Synta.

Transfer Agent and Registrar

The transfer agent and registrar for our preferred stock will be set forth in the applicable prospectus supplement.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus. While the terms we have summarized below will apply generally to any future debt securities we may offer pursuant to this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. If we so indicate in a prospectus supplement, the terms of any debt securities offered under such prospectus supplement may differ from the terms we describe below, and to the extent the terms set forth in a prospectus supplement differ from the terms described below, the terms set forth in the prospectus supplement shall control.

We may sell from time to time, in one or more offerings under this prospectus, debt securities, which may be senior or subordinated. We will issue any such senior debt securities under a senior indenture that we will enter into with a trustee to be named in the senior indenture. We will issue any such subordinated debt securities under a subordinated indenture, which we will enter into with a trustee to be named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, of which this prospectus is a part. We use the term "indentures" to refer to either the senior indenture or the subordinated indenture, as applicable. The indentures will be qualified under the Trust Indenture Act of 1939, as in effect on the date of the indenture. We use the term "debenture trustee" to refer to either the trustee under the senior indenture or the trustee under the subordinated indenture, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all the provisions of the indenture applicable to a particular series of debt securities.

General

Each indenture provides that debt securities may be issued from time to time in one or more series and may be denominated and payable in foreign currencies or units based on or relating to foreign currencies. Neither indenture limits the amount of debt securities that may be issued thereunder, and each indenture provides that the specific terms of any series of debt securities shall be set forth in, or determined pursuant to, an authorizing resolution and/or a supplemental indenture, if any, relating to such series.

We will describe in each prospectus supplement the following terms relating to a series of debt securities:

- the title or designation;
- the aggregate principal amount and any limit on the amount that may be issued;
- the currency or units based on or relating to currencies in which debt securities of such series are denominated and the currency or units in which principal or interest or both will or may be payable;
- whether we will issue the series of debt securities in global form, the terms of any global securities and who the depository will be;
- the maturity date and the date or dates on which principal will be payable;
- the interest rate, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the date or dates interest will be payable and the record dates for interest payment dates or the method for determining such dates;

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- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- the terms of the subordination of any series of subordinated debt;
- the place or places where payments will be payable;
- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- the date, if any, after which, and the price at which, we may, at our option, redeem the series of debt securities pursuant to any optional redemption provisions;
- the date, if any, on which, and the price at which we are obligated, pursuant to any mandatory sinking fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities;
- whether the indenture will restrict our ability to pay dividends, or will require us to maintain any asset ratios or reserves;
- whether we will be restricted from incurring any additional indebtedness;
- a discussion on any material or special U.S. federal income tax considerations applicable to a series of debt securities;
- the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

Conversion or Exchange Rights

We will set forth in the prospectus supplement the terms, if any, on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale; No Protection in Event of a Change of Control or Highly Leveraged Transaction

The indentures do not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets must assume all of our obligations under the indentures or the debt securities, as appropriate.

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions that may afford holders of the debt securities protection in the event we have a change of control or in the event of a highly leveraged transaction (whether or not such transaction results in a change of control), which could adversely affect holders of debt securities.

Events of Default Under the Indenture

The following are events of default under the indentures with respect to any series of debt securities that we may issue:

- if we fail to pay interest when due and our failure continues for 90 days and the time for payment has not been extended or deferred;
- if we fail to pay the principal, or premium, if any, when due and the time for payment has not been extended or delayed;
- if we fail to observe or perform any other covenant set forth in the debt securities of such series or the applicable indentures, other than a covenant specifically relating to and for the benefit of holders of another series of debt securities, and our failure continues for 90 days after we receive written notice from the debenture trustee or holders of not less than a majority in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur as to us.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an event of default with respect to any other series of debt securities. The occurrence of an event of default may constitute an event of default under any bank credit agreements we may have in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

If an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the debenture trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) of and premium and accrued and unpaid interest, if any, on all debt securities of that series. Before a judgment or decree for payment of the money due has been obtained with respect to debt securities of any series, the holders of a majority in principal amount of the outstanding debt securities of that series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal, premium, if any, and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the applicable indenture (including payments or deposits in respect of principal, premium or interest that had become due other than as a result of such acceleration). We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an event of default.

Subject to the terms of the indentures, if an event of default under an indenture shall occur and be continuing, the debenture trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the debenture trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the debenture trustee, or exercising any trust or power conferred on the debenture trustee, with respect to the debt securities of that series, provided that:

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

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

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

- the holder previously has given written notice to the debenture trustee of a continuing event of default with respect to that series;
- the holders of at least a majority in aggregate principal amount of the outstanding debt securities of that series have made written request, and such holders have offered reasonable indemnity to the debenture trustee to institute the proceeding as trustee; and
- the debenture trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series (or at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) other conflicting directions within 60 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the applicable debenture trustee regarding our compliance with specified covenants in the applicable indenture.

Modification of Indenture; Waiver

The debenture trustee and we may change the applicable indenture without the consent of any holders with respect to specific matters, including:

- to fix any ambiguity, defect or inconsistency in the indenture; and
- to change anything that does not materially adversely affect the interests of any holder of debt securities of any series issued pursuant to such indenture.

In addition, under the indentures, the rights of holders of a series of debt securities may be changed by us and the debenture trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) that is affected. However, the debenture trustee and we may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of the series of debt securities;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or any premium payable upon the redemption of any debt securities;
- reducing the principal amount of discount securities payable upon acceleration of maturity;
- making the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment or waiver.

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series (or, at a meeting of holders of such series at which a quorum

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is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series or in respect of a covenant or provision, which cannot be modified or amended without the consent of the holder of each outstanding debt security of the series affected; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for obligations to:

- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

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

Form, Exchange, and Transfer

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

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

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

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

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

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Debenture Trustee

The debenture trustee, other than during the occurrence and continuance of an event of default under the applicable indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the debenture trustee under such indenture must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the debenture trustee is under no obligation to exercise any of the powers given it by the indentures at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

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

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

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

Governing Law

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

Subordination of Subordinated Debt Securities

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

DESCRIPTION OF WARRANTS

General

We may issue warrants to purchase shares of our common stock, preferred stock and/or debt securities in one or more series together with other securities or separately, as described in the applicable prospectus supplement. Below is a description of certain general terms and provisions of the warrants that we may offer. Particular terms of the warrants will be described in the warrant agreements and the prospectus supplement relating to the warrants.

The applicable prospectus supplement will contain, where applicable, the following terms of and other information relating to the warrants:

- the specific designation and aggregate number of, and the price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the designation, amount and terms of the securities purchasable upon exercise of the warrants;
- if applicable, the exercise price for shares of our common stock and the number of shares of common stock to be received upon exercise of the warrants;
- if applicable, the exercise price for shares of our preferred stock, the number of shares of preferred stock to be received upon exercise, and a description of that series of our preferred stock;
- if applicable, the exercise price for our debt securities, the amount of debt securities to be received upon exercise, and a description of that series of debt securities;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- whether the warrants will be issued in fully registered form or bearer form, in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- if applicable, the date from and after which the warrants and the common stock, preferred stock and/or debt securities will be separately transferable;

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- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the anti-dilution provisions of the warrants, if any;
- any redemption or call provisions;
- whether the warrants may be sold separately or with other securities as parts of units; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants.

Transfer Agent and Registrar

The transfer agent and registrar for any warrants will be set forth in the applicable prospectus supplement.

DESCRIPTION OF RIGHTS

General

We may issue rights to our stockholders to purchase shares of our common stock, preferred stock or the other securities described in this prospectus. We may offer rights separately or together with one or more additional rights, debt securities, preferred stock, common stock, warrants or purchase contracts, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. Each series of rights will be issued under a separate rights agreement to be entered into between us and a bank or trust company, as rights agent. The rights agent will act solely as our agent in connection with the certificates relating to the rights of the series of certificates and will not assume any obligation or relationship of agency or trust for or with any holders of rights certificates or beneficial owners of rights. The following description sets forth certain general terms and provisions of the rights to which any prospectus supplement may relate. The particular terms of the rights to which any prospectus supplement may relate and the extent, if any, to which the general provisions may apply to the rights so offered will be described in the applicable prospectus supplement. To the extent that any particular terms of the rights, rights agreement or rights certificates described in a prospectus supplement differ from any of the terms described below, then the terms described below will be deemed to have been superseded by that prospectus supplement. We encourage you to read the applicable rights agreement and rights certificate for additional information before you decide whether to purchase any of our rights.

We will provide in a prospectus supplement the following terms of the rights being issued:

- the date of determining the stockholders entitled to the rights distribution;
- the aggregate number of shares of common stock, preferred stock or other securities purchasable upon exercise of the rights;
- the exercise price;
- the aggregate number of rights issued;
- whether the rights are transferrable and the date, if any, on and after which the rights may be separately transferred;
- the date on which the right to exercise the rights will commence, and the date on which the right to exercise the rights will expire;
- the method by which holders of rights will be entitled to exercise;

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- the conditions to the completion of the offering, if any;
- the withdrawal, termination and cancellation rights, if any;
- whether there are any backstop or standby purchaser or purchasers and the terms of their commitment, if any;
- whether stockholders are entitled to oversubscription rights, if any;
- any applicable U.S. federal income tax considerations; and
- any other terms of the rights, including terms, procedures and limitations relating to the distribution, exchange and exercise of the rights, as applicable.

Each right will entitle the holder of rights to purchase for cash the principal amount of shares of common stock, preferred stock or other securities at the exercise price provided in the applicable prospectus supplement. Rights may be exercised at any time up to the close of business on the expiration date for the rights provided in the applicable prospectus supplement.

Holders may exercise rights as described in the applicable prospectus supplement. Upon receipt of payment and the rights certificate properly completed and duly executed at the corporate trust office of the rights agent or any other office indicated in the prospectus supplement, we will, as soon as practicable, forward the shares of common stock, preferred stock or other securities, as applicable, purchasable upon exercise of the rights. If less than all of the rights issued in any rights offering are exercised, we may offer any unsubscribed securities directly to persons other than stockholders, to or through agents, underwriters or dealers or through a combination of such methods, including pursuant to standby arrangements, as described in the applicable prospectus supplement.

Rights Agent

The rights agent for any rights we offer will be set forth in the applicable prospectus supplement.

DESCRIPTION OF PURCHASE CONTRACTS

We may issue purchase contracts, including contracts obligating holders to purchase from us, and for us to sell to holders, a specific or variable number of our debt securities, shares of common stock, preferred stock, warrants or rights, or securities of an entity unaffiliated with us, or any combination of the above, at a future date or dates. Alternatively, the purchase contracts may obligate us to purchase from holders, and obligate holders to sell to us, a specific or variable number of our debt securities, shares of common stock, preferred stock, warrants, rights or other property, or any combination of the above. The price of the securities or other property subject to the purchase contracts may be fixed at the time the purchase contracts are issued or may be determined by reference to a specific formula described in the purchase contracts. We may issue purchase contracts separately or as a part of units each consisting of a purchase contract and one or more of our other securities described in this prospectus or securities of third parties, including U.S. Treasury securities, securing the holder's obligations under the purchase contract. The purchase contracts may require us to make periodic payments to holders or vice versa and the payments may be unsecured or pre-funded on some basis. The purchase contracts may require holders to secure the holder's obligations in a manner specified in the applicable prospectus supplement.

The applicable prospectus supplement will describe the terms of any purchase contracts in respect of which this prospectus is being delivered, including, to the extent applicable, the following:

- whether the purchase contracts obligate the holder or us to purchase or sell, or both purchase and sell, the securities subject to purchase under the purchase contract, and the nature and amount of each of those securities, or the method of determining those amounts;

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- whether the purchase contracts are to be prepaid;
- whether the purchase contracts are to be settled by delivery, or by reference or linkage to the value, performance or level of the securities subject to purchase under the purchase contract;
- any acceleration, cancellation, termination or other provisions relating to the settlement of the purchase contracts;
- any applicable U.S. federal income tax considerations; and
- whether the purchase contracts will be issued in fully registered or global form.

The preceding description sets forth certain general terms and provisions of the purchase contracts to which any prospectus supplement may relate. The particular terms of the purchase contracts to which any prospectus supplement may relate and the extent, if any, to which the general provisions may apply to the purchase contracts so offered will be described in the applicable prospectus supplement. To the extent that any particular terms of the purchase contracts described in a prospectus supplement differ from any of the terms described above, then the terms described above will be deemed to have been superseded by that prospectus supplement. We encourage you to read the applicable purchase contract for additional information before you decide whether to purchase any of our purchase contracts.

DESCRIPTION OF UNITS

The following description, together with the additional information that we include in any applicable prospectus supplements summarizes the material terms and provisions of the units that we may offer under this prospectus. While the terms we have summarized below will apply generally to any units that we may offer under this prospectus, we will describe the particular terms of any series of units in more detail in the applicable prospectus supplement. The terms of any units offered under a prospectus supplement may differ from the terms described below.

We will incorporate by reference from reports that we file with the SEC, the form of unit agreement that describes the terms of the series of units we are offering, and any supplemental agreements, before the issuance of the related series of units. The following summaries of material terms and provisions of the units are subject to, and qualified in their entirety by reference to, all the provisions of the unit agreement and any supplemental agreements applicable to a particular series of units. We urge you to read the applicable prospectus supplements related to the particular series of units that we may offer under this prospectus, as well as any related free writing prospectuses and the complete unit agreement and any supplemental agreements that contain the terms of the units.

General

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

We will describe in the applicable prospectus supplement the terms of the series of units being offered, including:

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

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- any provisions of the governing unit agreement that differ from those described below; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

The provisions described in this section, as well as those set forth in any prospectus supplement or as described under "Description of Common Stock," "Description of Preferred Stock," "Description of Debt Securities," "Description of Warrants," "Description of Rights," "Description of Purchase Contracts" and "Description of Units" will apply to each unit, as applicable, and to any common stock, preferred stock, debt security, warrant, right or purchase contract included in each unit, as applicable.

Unit Agent

The name and address of the unit agent for any units we offer will be set forth in the applicable prospectus supplement.

Issuance in Series

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

Enforceability of Rights by Holders of Units

Each unit agent will act solely as our agent under the applicable unit agreement and will not assume any obligation or relationship of agency or trust with any holder of any unit. A single bank or trust company may act as unit agent for more than one series of units. A unit agent will have no duty or responsibility in case of any default by us under the applicable unit agreement or unit, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a unit may, without the consent of the related unit agent or the holder of any other unit, enforce by appropriate legal action its rights as holder under any security included in the unit.

CERTAIN PROVISIONS OF DELAWARE LAW AND OF THE COMPANY'S CERTIFICATE OF INCORPORATION AND BYLAWS

Anti-Takeover Provisions of our Certificate of Incorporation and Bylaws

In addition to the board of directors' ability to issue shares of preferred stock, our restated certificate of incorporation and restated bylaws contain other provisions that are intended to enhance the likelihood of continuity and stability in the composition of the board of directors and which may have the effect of delaying, deferring or preventing a future takeover or change in control of our company unless such takeover or change in control is approved by our board of directors.

These provisions, summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed 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 potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Classified board of directors; removal of directors for cause. Our restated certificate of incorporation and restated bylaws provide for our board of directors to be divided into three classes serving staggered terms. At each annual meeting of stockholders, directors elected to succeed those directors whose terms expire are elected for a three-year term of office. All directors elected to our classified board of directors will serve until the election and qualification of their respective successors or their earlier resignation or removal. The board of directors is authorized to create new directorships and to fill such positions so created and is permitted to specify the class to which any such new position

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is assigned. The person filling such position would serve for the term applicable to that class. The board of directors (or its remaining members, even if less than a quorum) is also empowered to fill vacancies on the board of directors occurring for any reason for the remainder of the term of the class of directors in which the vacancy occurred. Members of the board of directors may only be removed for cause and only by the affirmative vote of 80% of our outstanding voting stock. These provisions are likely to increase the time required for stockholders to change the composition of the board of directors. For example, in general, at least two annual meetings will be necessary for stockholders to effect a change in a majority of the members of the board of directors. The provision for a classified board could prevent a party who acquires control of a majority of our outstanding common stock from obtaining control of our board of directors until our second annual stockholders meeting following the date the acquirer obtains the controlling stock interest. The classified board provision could have the effect of discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us and could increase the likelihood that incumbent directors will retain their positions.

Advance notice provisions for stockholder proposals. Our restated bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors, as well as procedures for including proposed nominations at special meetings at which directors are to be elected. Stockholders at our annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board or by a stockholder who was a stockholder of record on the record date for the meeting, who is entitled to vote at the meeting and who has given to our secretary timely written notice, in proper form, of the stockholder's intention to bring that business before the meeting, and who has complied with the procedures and requirements set forth in the bylaws. Although our bylaws do not give our board of directors the power to approve or disapprove stockholder nominations of candidates or proposals regarding other business to be conducted at a special or annual meeting, our bylaws may have the effect of precluding the conduct of some business at a meeting if the proper procedures are not followed or may discourage or defer a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of us.

Special meetings of stockholders. Special meetings of the stockholders may be called only by our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors. Stockholders are not permitted to call a special meeting or to require our board of directors to call a special meeting.

No stockholder action by written consent. Our restated certificate of incorporation and restated bylaws do not permit our stockholders to act by written consent. As a result, any action to be effected by our stockholders must be effected at a duly called annual or special meeting of the stockholders.

Super-majority stockholder vote required for certain actions. The Delaware General Corporation Law provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws, unless the corporation's certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our restated certificate of incorporation requires the affirmative vote of the holders of at least 80% of our outstanding voting stock to amend or repeal certain provisions of our restated certificate of incorporation. This 80% stockholder vote would be in addition to any separate class vote that might in the future be required pursuant to the terms of any preferred stock that might then be outstanding. In addition, an 80% vote is also required for any amendment to, or repeal of, our restated bylaws by the stockholders. Our restated bylaws may be amended or repealed by a vote of a majority of the total number of authorized directors.

Provisions of Delaware Law Governing Business Combinations

We are subject to the "business combination" provisions of Section 203 of the Delaware General Corporation Law. In general, such provisions prohibit a publicly held Delaware corporation from engaging in any "business combination" transactions with any "interested stockholder" for a period of three years after the date on which the person became an "interested stockholder," unless:

- prior to such date, the board of directors approved either the "business combination" or the transaction which resulted in the "interested stockholder" obtaining such status;
- upon consummation of the transaction which 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 voting stock outstanding (but not the outstanding voting stock owned by the "interested stockholder") those shares owned by (a) persons who are directors and also officers and (b) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- at or subsequent to such time the "business combination" is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66²/₃% of the outstanding voting stock which is not owned by the "interested stockholder."

A "business combination" is defined to include mergers, asset sales and other transactions resulting in financial benefit to a stockholder. In general, an "interested stockholder" is a person who, together with affiliates and associates, owns 15% or more of a corporation's voting stock or within three years did own 15% or more of a corporation's voting stock. The statute could prohibit or delay mergers or other takeover or change in control attempts with respect to us and, accordingly, may discourage attempts to acquire us.

Limitations on Liability and Indemnification of Officers and Directors

Our restated certificate of incorporation limits the liability of our officers and directors to the fullest extent permitted by the Delaware General Corporation Law, and our restated certificate of incorporation and restated bylaws provide that we will indemnify our officers and directors to the fullest extent permitted by such law. We have also entered into indemnification agreements with our officers and directors and expect to enter into a similar agreement with any new officers and directors.

LEGAL MATTERS

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, will pass upon the validity of the issuance of the securities offered by this prospectus.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2014, and the effectiveness of our internal control over financial reporting as of December 31, 2014, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference facilities at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference facilities. SEC filings are also available at the SEC's web site at <http://www.sec.gov>. Our common stock is listed on The NASDAQ Global Market, and you can read and inspect our filings at the offices of the Financial Industry Regulatory Authority at 1735 K Street, Washington, D.C. 20006.

This prospectus is only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act of 1933, as amended, and therefore omits certain information contained in the registration statement. We have also filed exhibits and schedules with the registration statement that are excluded from this prospectus, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document. You may inspect a copy of the registration statement, including the exhibits and schedules, without charge, at the public reference room or obtain a copy from the SEC upon payment of the fees prescribed by the SEC.

We also maintain a website at www.syntapharma.com, through which you can access our SEC filings. The information set forth on our website is not part of this prospectus.

INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" information that we file with them. Incorporation by reference allows us to disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We filed a registration statement on Form S-3 under the Securities Act of 1933, as amended, with the SEC with respect to the securities we may offer pursuant to this prospectus. This prospectus omits certain information contained in the registration statement, as permitted by the SEC. You should refer to the registration statement, including the exhibits, for further information about us and the securities we may offer pursuant to this prospectus. Statements in this prospectus regarding the provisions of certain documents filed with, or incorporated by reference in, the registration statement are not necessarily complete and each statement is qualified in all respects by that reference. Copies of all or any part of the registration statement, including the documents incorporated by reference or the exhibits, may be obtained upon payment of the prescribed rates at the offices of the SEC listed above in "Where You Can Find More Information." The documents we are incorporating by reference are:

- our Annual Report on Form 10-K for the year ended December 31, 2014 filed on March 12, 2015;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2015 and June 30, 2015 filed on May 7, 2015 and August 6, 2015, respectively;
- our Current Reports on Form 8-K filed on February 5, 2015, March 6, 2015, April 1, 2015, April 6, 2015, April 27, 2015 and June 15, 2015;
- the portions of our Definitive Proxy Statement on Schedule 14A filed on April 30, 2015 that are deemed "filed" with the SEC under the Exchange Act;
- the description of our common stock contained in our Registration Statement on Form 8-A filed on January 26, 2007, including any amendment or report filed for the purpose of updating such description; and

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- all reports and other documents subsequently filed by us pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Exchange Act after the date of this prospectus and prior to the termination or completion of the offering of securities under this prospectus shall be deemed to be incorporated by reference in this prospectus and to be a part hereof from the date of filing such reports and other documents.

The SEC file number for each of the documents listed above is 001-33277.

Any statement contained in this prospectus or in a document incorporated or deemed to be incorporated by reference into this prospectus will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or any other subsequently filed document that is deemed to be incorporated by reference into this prospectus modifies or supersedes the statement. Any statement so modified or superseded will not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

You may request, orally or in writing, a copy of any or all of the documents incorporated herein by reference. These documents will be provided to you at no cost, by contacting: Investor Relations, Synta Pharmaceuticals Corp., 45 Hartwell Avenue, Lexington, MA 02421, (781) 274-8200.

You should rely only on information contained in, or incorporated by reference into, this prospectus and any prospectus supplement. We have not authorized anyone to provide you with information different from that contained in this prospectus or incorporated by reference in this prospectus. We are not making offers to sell the securities in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.



\$100,000,000

Common Stock

PROSPECTUS SUPPLEMENT

Cowen and Company

October 16, 2015
