

SYNERGY PHARMACEUTICALS, INC.

Form S-3

July 02, 2015

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As filed with the Securities and Exchange Commission on July 2, 2015

Registration No. 333-

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM S-3

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

Synergy Pharmaceuticals Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction
of incorporation or organization)

33-0505269
(I.R.S. Employer
Identification No.)

420 Lexington Avenue, Suite 2012

New York, New York 10170

(212)297-0020

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

Gary S. Jacob, Ph.D.

Chief Executive Officer

Synergy Pharmaceuticals Inc.

420 Lexington Avenue, Suite 2012

New York, NY 10170

(212)297-0020

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

With copies to:

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

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

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

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- (4) The registration fee has been calculated in accordance with Rule 457(o) under the Securities Act of 1933, as amended.

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

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

SUBJECT TO COMPLETION, DATED JULY 2, 2015

PROSPECTUS

SYNERGY PHARMACEUTICALS INC.

\$250,000,000

Common Stock

Preferred Stock

Debt Securities

Warrants

Units

We may offer and sell, from time to time in one or more offerings, any combination of common stock, preferred stock, debt securities, warrants to purchase common stock, preferred stock or debt securities, or any combination of the foregoing, either individually or as units comprised of one or more of the other securities, having an aggregate initial offering price not exceeding \$250,000,000.

This prospectus provides a general description of the securities we may offer. Each time we sell a particular class or series of securities, we will provide specific terms of the securities offered in a supplement to this prospectus. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. You should read carefully this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as any documents incorporated by reference herein or therein before you invest in any of our securities.

This prospectus may not be used to offer or sell our securities unless accompanied by a prospectus supplement relating to the offered securities.

Our common stock is presently listed on The NASDAQ Global Select Market under the symbol SGYP. On July 1, 2015, the last reported sale price of our common stock was \$9.10. The applicable prospectus supplement will contain information, where applicable, as to any other listing on The NASDAQ Global Select Market or any securities market or other exchange of the securities, if any, covered by the prospectus supplement.

These securities may be sold directly by us, through dealers or agents designated from time to time, to or through underwriters, dealers or through a combination of these methods on a continuous or delayed basis. See Plan of Distribution in this prospectus. We may also describe the plan of distribution for any particular offering of our securities in a prospectus supplement. If any agents, underwriters or dealers are involved in the sale of any securities in respect of which this prospectus is being delivered, we will disclose their names and the nature of our arrangements with them in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from any such sale will also be included in a prospectus supplement.

Investing in our securities involves various risks. See Risk Factors contained herein for more information on these risks. Additional risks will be described in the related prospectus supplements under the heading Risk Factors. You should review that section of the related prospectus supplements for a discussion of matters that investors in our securities should consider.

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 or any accompanying prospectus supplement. Any representation to the contrary is a criminal offense.

The date of this Prospectus is _____, 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 (the SEC) under the Securities Act of 1933, as amended (the Securities Act) using a shelf registration process. Under this shelf registration process, we may from time to time sell common stock, preferred stock, debt securities or warrants to purchase common stock, preferred stock or debt securities, or any combination of the foregoing, either individually or as units comprised of one or more of the other securities, in one or more offerings up to a total dollar amount of \$250,000,000. We have provided to you in this prospectus a general description of the securities we may offer. Each time we sell securities under this shelf registration, we will, to the extent required by law, provide a prospectus supplement that will contain specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in any documents that we have incorporated by reference into this prospectus. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement or any related free writing prospectus, you should rely on the information in the prospectus supplement or the related free writing prospectus; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in this prospectus or any prospectus supplement or any related free writing prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

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

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

Company References

In this prospectus, Synergy, the Company, we, us, and our refer to Synergy Pharmaceuticals Inc., a Delaware corporation, unless the context otherwise requires.

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OUR BUSINESS

Business Overview

We are a biopharmaceutical company focused primarily on the development of drugs to treat gastrointestinal, or GI, disorders and diseases. Our lead product candidate is plecanatide (formerly called SP-304), a phase 3 guanylate cyclase C, or GC-C, receptor agonist, designed to treat GI disorders, primarily chronic idiopathic constipation, or CIC, and constipation-predominant irritable bowel syndrome, or IBS-C. CIC and IBS-C are functional gastrointestinal disorders that afflict millions of individuals worldwide. CIC is primarily characterized by constipation symptoms with straining, bloating and abdominal discomfort reported by a majority of such patients. IBS-C is characterized by frequent and recurring abdominal pain and/or discomfort associated with chronic constipation. Plecanatide has completed two phase 3 registration trials in CIC patients, and has begun the first of two phase 3 registration trials in IBS-C patients. Our second drug in the clinic, dolcanatide (formerly called SP-333) is a next-generation uroguanylin analog in development for the treatment of opioid induced constipation, or OIC, and mild-to-moderate ulcerative colitis. Dolcanatide is designed to be a highly potent and proteolytically stable analog of the naturally occurring GI peptide, uroguanylin, displaying significant resistance to proteolysis in gastric intestinal fluids. We completed phase 1 single- and multiple-ascending dose studies in healthy volunteers, as well as reporting positive data from a phase 2 clinical trial of dolcanatide in OIC patients. We have also announced the start of a phase 1b proof-of-concept trial of dolcanatide in patients with ulcerative colitis. We have additionally been developing a unique formulation of dolcanatide for use in patients with ulcerative colitis.

Recent Developments

On January 8, 2015 and January 29, 2015 we announced that we had completed patient enrollment in the first and second of two pivotal phase 3 trials, respectively, which are evaluating the safety and efficacy of two plecanatide doses (3.0 and 6.0 mg) in patients with CIC. Each trial is a randomized, 12-week, double-blind, placebo-controlled phase 3 trial evaluating plecanatide, once-daily oral tablets, in approximately 1350 adult patients with CIC.

On June 17, 2015 we announced positive top-line results from the first of two pivotal phase 3 clinical trials evaluating the efficacy and safety of two different plecanatide treatment doses (3.0 mg and 6.0 mg), taken as a tablet once-a-day, in 1,346 adult patients with chronic idiopathic constipation (CIC). Preliminary analysis of the data indicates that both plecanatide 3.0 mg and 6.0 mg doses met the study's primary endpoint and demonstrated statistical significance in the proportion of patients in the intention-to-treat population who were durable overall responders compared to placebo during the 12-week treatment period (21.0% in 3.0 mg and 19.5% in 6.0 mg dose groups compared to 10.2% in placebo; $p < 0.001$ for both doses). The durable overall responder endpoint is the current FDA endpoint required for U.S. approval in CIC. Plecanatide would be the first drug approved for CIC using the more stringent regulatory requirement for durability in the response. Notably, plecanatide was safe and well tolerated at both doses; the most common adverse event was diarrhea, which occurred in 5.9% of patients in 3.0 mg and 5.5% of patients in 6.0 mg dose groups compared to 1.3% of placebo-treated patients.

We expect to release top-line results from the second phase 3 CIC trial in the third quarter of 2015. In the fourth quarter of 2015, we plan to file our first new drug application (NDA) with FDA for plecanatide to treat CIC.

On June 23, 2015 we announced the initiation of the second of two pivotal phase 3 clinical trials evaluating the efficacy and safety of two different plecanatide treatment doses (3.0 mg and 6.0 mg), taken as a tablet once-a-day, in patients with irritable bowel syndrome with constipation (IBS-C). The phase 3 IBS-C program includes two randomized, 12-week, double-blind, placebo-controlled pivotal trials conducted in the United States and each trial is expected to enroll approximately 1050 adult patients with IBS-C. Patients with IBS-C are defined by Rome III Criteria as having a history of constipation and abdominal pain for at least 6 months, including hard or lumpy stools for 25% or more of defecations, loose or watery stools for 25% or less of defecations, and abdominal pain or discomfort for 3 days or more per month for the last 3 months. The primary efficacy endpoint for both trials is the percentage of patients who are Overall Responders during the 12 week treatment period. An Overall Responder, as defined by the FDA, is a patient who is a weekly responder (i.e. meets both the abdominal pain intensity reduction and stool frequency increase criteria in the same week) for at least 6 of the 12 treatment weeks.

Plecanatide

Plecanatide is a synthetic analog of uroguanylin, a natural human peptide that regulates ion and fluid transport in the intestine. Orally-administered, plecanatide binds to the same receptors on the inside of the gastrointestinal tract as uroguanylin, and we believe it is capable of restoring the normal balance of fluid, thus restoring the regular function of the intestine in patients suffering from GI disorders such as CIC and IBS-C.

Constipation can be the by-product of other disease states, as well as due to certain drug therapies (e.g., narcotics) or anatomic anomalies. CIC, in contrast, is defined as having no identifiable causes. Patients diagnosed with CIC have experienced symptoms for 6 months or more, and commonly have less than 3 bowel movements a week and often less than one. They suffer from very hard stool

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and abdominal symptoms such as bloating, discomfort, gas, and a feeling of incomplete evacuation. The prescription drugs currently available have significant side effects and are generally only effective in less than half of patients treated. Plecanatide offers hope for a more effective and tolerable treatment that can relieve the significant burden which CIC places on patients' lives.

On January 2, 2013, we announced positive results from our large phase 2 multicenter clinical trial of our lead investigational drug plecanatide in patients with CIC. On May 15, 2013, at Digestive Disease Week 2013, we presented a late-breaking abstract, the title of which is: "Plecanatide, a Novel Guanylate Cyclase C (GC-C) Receptor Agonist, is Efficacious and Safe in Patients with Chronic Idiopathic Constipation (CIC): Results from a 951-Patient, 12-Week, Multi-Center Trial."

Phase 3 Clinical Trials for CIC

On November 13, 2013, we announced the start of the first of two planned pivotal Phase 3 clinical trials to confirm the safety and efficacy of plecanatide in adult patients with CIC. The pivotal Phase 3 trial is a randomized, double-blind, clinical trial to compare a 12-week, dose-ranging regimen of plecanatide (3.0 and 6.0mg) against placebo in adult patients with CIC. The study was expected to be conducted at approximately 180 sites in the United States and Canada and we expected to enroll approximately 1,350 patients with CIC. The primary endpoint of the study is the proportion of patients who are overall responders for the 12-week treatment period.

On April 28, 2014, we initiated our second pivotal Phase 3 clinical trial for plecanatide in CIC patients. The primary objective of this trial is to confirm the safety and efficacy of plecanatide, a GC-C receptor agonist and once-daily oral treatment, in adult patients with CIC. This Phase 3 trial is a randomized, double-blind clinical trial to compare a 12-week, dose-ranging regimen of plecanatide (3.0 and 6.0mg) against placebo in adult patients with CIC. The study was expected to be conducted at approximately 180 sites in the United States and we expected to enroll approximately 1,350 patients with CIC. The primary endpoint of the study is the proportion of patients who are overall responders for the 12-week treatment period.

On January 8, 2015 and January 29, 2015 we announced that we had completed patient enrollment in the first and second of two pivotal phase 3 trials, respectively, which are evaluating the safety and efficacy of two plecanatide doses (3.0 and 6.0 mg) in patients with CIC. Each trial is a randomized, 12-week, double-blind, placebo-controlled phase 3 trial evaluating approximately 1350 adult patients with CIC.

On June 17, 2015 we announced positive top-line results from the first of two pivotal phase 3 clinical trials evaluating the efficacy and safety of two different plecanatide treatment doses (3.0 mg and 6.0 mg), taken as a tablet once-a-day, in 1,346 adult patients with chronic idiopathic constipation (CIC). Preliminary analysis of the data indicates that both plecanatide 3.0 mg and 6.0 mg doses met the study's primary endpoint and demonstrated statistical significance in the proportion of patients in the intention-to-treat population who were durable overall responders compared to placebo during the 12-week treatment period (21.0% in 3.0 mg and 19.5% in 6.0 mg dose groups compared to 10.2% in placebo; $p < 0.001$ for both doses). The durable overall responder endpoint is the current FDA endpoint required for U.S. approval in CIC. Plecanatide would be the first drug approved for CIC using the more stringent regulatory requirement for durability in the response. Notably, plecanatide was safe and well tolerated at both doses; the most common adverse event was diarrhea, which occurred in 5.9% of patients in 3.0 mg and 5.5% of patients in 6.0 mg dose groups compared to 1.3% of placebo-treated patients.

We expect to release top-line results from the second phase 3 CIC trial in the third quarter of 2015. In the fourth quarter of 2015, we plan to file our first new drug application (NDA) with FDA for plecanatide to treat CIC.

Phase 2b Clinical Trial for IBS-C

In addition to CIC, plecanatide is also being developed to treat IBS-C. IBS is generally characterized by symptoms of abdominal pain or discomfort such as cramping, bloating, gas, and constipation or diarrhea or both. IBS-C is the subtype of IBS that plecanatide is being developed to treat. IBS is one of the most commonly diagnosed GI illnesses in the United States. As many as 14% of, or up to 42 million, adult Americans suffer from IBS. Depending on the criteria used to define bowel habit predominance, it is estimated that 16% to 30% of IBS patients (approximately 7 to 13 million) experience symptoms consistent with the IBS-C subtype.

IBS profoundly impacts patients' physical, social and working lives. A quarter of patients describe their abdominal pain as constant. IBS is one of the most common reasons for work or school absenteeism, second only to the common cold. Fewer than 1 in 10 patients say they are satisfied with available IBS treatments. Healthcare systems spend billions of dollars annually to diagnose and treat this disorder. In the U.S., the annual cost of IBS treatment is estimated to be as much as \$8 billion in direct medical costs, including doctor and hospital visits and diagnostic procedures.

On December 27, 2012, we commenced a Phase 2b dose-ranging trial of plecanatide to treat patients with IBS-C. This study was conducted at 70 sites in the U.S. To qualify for enrollment, patients had to meet the Rome III criteria for IBS-C as modified for this study. Abdominal pain is a major part of this syndrome and patients need to have pain scores of 3 or more (on a scale of 1 to 10) for 3 days in each of the two pre-treatment weeks. Qualified patients were randomized to receive 0.3, 1, 3 or 9 mg of plecanatide or placebo once daily for 12 weeks, and were seen at the clinical sites once a month during the study.

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On April 30, 2014, we announced positive top-line results from our Phase 2b dose-ranging trial assessing plecanatide's safety and efficacy in 424 patients with IBS-C. The primary objective of this trial was to determine an effective, safe and well tolerated dose for plecanatide Phase 3 trials with IBS-C patients.

On October 20, 2014, we presented additional positive results from our phase 2b dose-ranging study assessing plecanatide's safety and efficacy in patients with IBS-C. The data were presented at the American College of Gastroenterology's 2014 Annual Scientific Meeting in Philadelphia, Pennsylvania. Plecanatide 1.0, 3.0 and 9.0 mg doses demonstrated statistically significant improvement in complete spontaneous bowel movement (CSBM) frequency, the trial's primary endpoint, with the highest two doses showing the greatest response (increase from baseline of 2.12, 2.74, 2.44 and 1.27 for 1.0, 3.0, 9.0 mg and placebo dose groups, respectively). Increasing efficacy was also observed at the higher dose range in other key secondary endpoints including overall responder rate (the end point for FDA approval) and abdominal pain responder rate. All doses were safe and well tolerated with no treatment-related serious adverse events.

Phase 3 Clinical Trials for IBS-C

On December 18, 2014, we announced the initiation of the first of two planned pivotal phase 3 clinical trials evaluating the safety and efficacy of 3.0 and 6.0 mg plecanatide, once-daily oral tablets, for the treatment of irritable bowel syndrome with constipation (IBS-C), consistent with the ongoing CIC registration trials. IBS-C patients successfully completing either of the 12-week placebo-controlled registration trials will be offered enrollment into a long-term safety trial in order to support the ongoing long-term safety database for the CIC indication.

On June 23, 2015 we announced the initiation of the second of two pivotal phase 3 clinical trials evaluating the efficacy and safety of two different plecanatide treatment doses (3.0 mg and 6.0 mg), taken as a tablet once-a-day, in patients with irritable bowel syndrome with constipation (IBS-C). The phase 3 IBS-C program includes two randomized, 12-week, double-blind, placebo-controlled pivotal trials conducted in the United States and each trial is expected to enroll approximately 1050 adult patients with IBS-C. Patients with IBS-C are defined by Rome III Criteria as having a history of constipation and abdominal pain for at least 6 months, including hard or lumpy stools for 25% or more of defecations, loose or watery stools for 25% or less of defecations, and abdominal pain or discomfort for 3 days or more per month for the last 3 months. The primary efficacy endpoint for both trials is the percentage of patients who are Overall Responders during the 12 week treatment period. An Overall Responder, as defined by the FDA, is a patient who is a weekly responder (i.e. meets both the abdominal pain intensity reduction and stool frequency increase criteria in the same week) for at least 6 of the 12 treatment weeks.

Dolcanatide (formerly called SP-333)

We are developing a second-generation GC-C receptor analog, dolcanatide, for the treatment of opioid induced constipation, or OIC, and for inflammatory bowel disease, or IBD. Dolcanatide is a synthetic analog of uroguanylin, a natriuretic peptide that is normally produced in the body's intestinal tract. Deficiency of this peptide is thought to be one of the primary reasons for the formation of polyps that can lead to colon cancer, as well as debilitating and difficult-to-treat GI inflammatory disorders such as ulcerative colitis and Crohn's disease.

On September 7, 2012, we submitted an Investigational New Drug, or IND, application for clinical evaluation of dolcanatide to treat IBD. On December 28, 2012, we successfully completed a Phase 1 placebo-controlled, dose-escalating, single-dose study of 70 healthy adult volunteers. In January 2013, we commenced a multiple-ascending oral-dosing study of healthy volunteers in a Phase 1 trial of dolcanatide, which was

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completed during the quarter ended June 30, 2013.

On October 30, 2013 we announced the start of the Phase 2 clinical trial to evaluate the safety and efficacy of dolcanatide in adult patients with OIC. The multi-center, randomized, double-blind clinical trial compares a 4-week, dose-ranging regimen of dolcanatide (1.0, 3.0 and 6.0mg) against placebo in adult patients taking opioid analgesics for chronic, non-cancer pain for at least three months.

On November 19, 2014 we announced positive top-line results from a phase 2 trial assessing safety, efficacy and dose-response of three different once-daily oral dolcanatide tablets (1.0, 3.0 and 6.0 mg) compared with placebo in 289 patients with OIC. Preliminary analysis of the data indicates dolcanatide met the study's primary endpoint and demonstrated statistically significant improvement in mean change from baseline in the number of spontaneous bowel movements (SBMs) during Week 4 of the treatment period. Dolcanatide was safe and well tolerated at all doses.

We continue to advance our ongoing phase 1b exploratory study of dolcanatide in patients with mild-to-moderate ulcerative colitis. Our double-blind, placebo-controlled, four-week study is being conducted in the United States and is expected to enroll approximately 24 patients.

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The Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and warrants to purchase any of such securities, either individually or in units, with a total value of up to \$250,000,000 from time to time under this prospectus, together with any applicable prospectus supplement and related free writing prospectus, at prices and on terms to be determined by market conditions at the time of offering. If we issue any debt securities at a discount from their original stated principal amount, then, for purposes of calculating the total dollar amount of all securities issued under this prospectus, we will treat the initial offering price of the debt securities as the total original principal amount of the debt securities. Each time we offer securities under this prospectus, we will provide offerees with a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities being offered, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity, if applicable;
- original issue discount, if any;
- rates and times of payment of interest or dividends, if any;
- redemption, conversion, exchange or sinking fund terms, if any;
- conversion or exchange prices or rates, if any, and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange;
- ranking;
- restrictive covenants, if any;

- voting or other rights, if any; and
- important United States federal income tax considerations.

Common Stock

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

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

We currently have authorized 350,000,000 shares of common stock, par value \$0.0001 per share. We may offer shares of our common stock either alone or underlying other registered securities convertible into or exercisable for our common stock. Holders of our common stock are entitled to such dividends as our Board of Directors may declare from time to time out of legally available funds, subject to the preferential rights of the holders of any shares of our preferred stock that are outstanding or that we may issue in the future. Currently, we do not pay any dividends on our common stock. Each holder of our common stock is entitled to one vote per share. In this prospectus, we provide a general description of, among other things, the rights and restrictions that apply to holders of our common stock.

Preferred Stock

We currently have authorized 20,000,000 shares of preferred stock, none of which are outstanding. Any authorized and undesignated shares of preferred stock may be issued from time to time in one or more series pursuant to a resolution or resolutions providing for such issue duly adopted by our Board of Directors (authority to do so being hereby expressly vested in the Board of Directors). The Board of Directors is further authorized, subject to limitations prescribed by law, to fix by resolution or resolutions the designations, powers, preferences and rights, and the qualifications, limitations or restrictions thereof, of any wholly unissued series of preferred stock, including without limitation authority to fix by resolution or resolutions the dividend rights, dividend rate, conversion rights, voting rights, rights and terms of redemption (including sinking fund provisions), redemption price or prices, and liquidation preferences of any such series, and the number of shares constituting any such series and the designation thereof, or any of the foregoing.

The rights, preferences, privileges and restrictions granted to or imposed upon any series of preferred stock that we offer and sell under this prospectus and applicable prospectus supplements will be set forth in a certificate of designation relating to the series. We will incorporate by reference into the registration statement of which this prospectus is a part the form of any certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of shares of that series of preferred stock. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the

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series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities

We may offer general debt obligations, which may be secured or unsecured, senior or subordinated and convertible into shares of our common stock. In this prospectus, we refer to the senior debt securities and the subordinated debt securities together as the debt securities. We may issue debt securities under a note purchase agreement or under an indenture to be entered between us and a trustee; forms of the senior and subordinated indentures are included as an exhibit to the registration statement of which this prospectus is a part. The indentures do not limit the amount of securities that may be issued under it and provides that debt securities may be issued in one or more series. The senior debt securities will have the same rank as all of our other indebtedness that is not subordinated. The subordinated debt securities will be subordinated to our senior debt on terms set forth in the applicable prospectus supplement. In addition, the subordinated debt securities will be effectively subordinated to creditors and preferred stockholders of our subsidiaries. Our Board of Directors will determine the terms of each series of debt securities being offered. This prospectus contains only general terms and provisions of the debt securities. The applicable prospectus supplement will describe the particular terms of the debt securities offered thereby. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of debt securities being offered, as well as the complete note agreements and/or indentures that contain the terms of the debt securities. Forms of indentures have been filed as exhibits to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of debt securities being offered will be incorporated by reference into the registration statement of which this prospectus is a part from reports we file with the SEC.

Warrants

We may offer warrants for the purchase of shares of our common stock or preferred stock or of debt securities. We may issue the warrants by themselves or together with common stock, preferred stock or debt securities, and the warrants may be attached to or separate from any offered securities. Each series of warrants will be issued under a separate warrant agreement to be entered into between us and the investors or a warrant agent. Our Board of Directors will determine the terms of the warrants. This prospectus contains only general terms and provisions of the warrants. The applicable prospectus supplement will describe the particular terms of the warrants being offered thereby. You should read any prospectus supplement and any free writing prospectus that we may authorize to be provided to you related to the series of warrants being offered, as well as the complete warrant agreements that contain the terms of the warrants. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference into the registration statement of which this prospectus is a part from reports we file with the SEC.

Units

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

terms and provisions and will be incorporated by reference into the registration statement of which this prospectus is a part from reports we file with the SEC.

Corporate Information

Our principal executive offices are located at 420 Lexington Avenue, Suite 2012, New York, New York 10170. Our telephone number is (212) 297-0020 and our website address is www.synergypharma.com. The information on our website is not a part of, and should not be construed as being incorporated by reference into, this prospectus or any prospectus supplement.

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RISK FACTORS

An investment in our securities involves a high degree of risk. This prospectus contains, and the prospectus supplement applicable to each offering of our securities, will contain a discussion of the risks applicable to an investment in our securities. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading "Risk Factors" in this prospectus and 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 Item 1A, "Risk Factors," in our Annual Report on Form 10-K for the fiscal year ended December 31, 2014 and any updates described in our Quarterly Reports on Form 10-Q, all of which are incorporated herein by reference, and may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future and any prospectus supplement related to a particular offering. 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. The occurrence of any of these known or unknown risks might cause you to lose all or part of your investment in the offered securities.

Risks Related to Our Business

We are at an early stage of development as a company and currently have no source of revenue and may never become profitable. Currently, we have no products approved for commercial sale and, to date, we have not generated any revenue.

Our ability to generate revenue depends heavily on:

- our ability to raise additional capital on a timely basis to continue to fund our clinical trials;
- demonstration in current and future clinical trials that our product candidates, plecanatide for the treatment of CIC and IBS-C and dolcanatide for the treatment of OIC and IBD, are safe and effective;
- our ability to seek and obtain regulatory approvals, including with respect to the indications we are seeking;
- successful manufacture and commercialization of our product candidates; and
- market acceptance of our products.

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All of our existing product candidates are in various stages of development and will require extensive additional preclinical and clinical evaluation, regulatory review and approval, significant marketing efforts and substantial investment before they could provide us with any revenue. As a result, even if we successfully develop, achieve regulatory approval and commercialize plecanatide, we will be unable to generate any revenue for many years, if at all. We do not anticipate that we will generate revenue for several years, at the earliest, or that we will achieve profitability for at least several years after generating material revenue, if at all. If we are unable to generate revenue, we will not become profitable, and we may be unable to continue our operations.

We will need to raise substantial additional capital to fund our operations, and our failure to obtain funding when needed may force us to delay, reduce or eliminate our lead product development programs or even discontinue or curtail our operations.

During the three months ended March 31, 2015, our operating activities used net cash of approximately \$23.1 million. During the twelve months ended December 31, 2014 and December 31, 2013, our operating activities used net cash of approximately \$89 million and \$52.6 million, respectively. Our available-for-sale securities as of March 31, 2015, December 31, 2014 and December 31, 2013 were \$99.9 million, \$50 million and \$50 million, respectively, which consists of U.S. Treasury securities with maturities of less than one year. In addition, as of March 31, 2015, December 31, 2014 and December 31, 2013 the amount of our cash and cash equivalents was \$78.7 million, \$146.5 million and \$18.1 million, respectively, consisting of checking accounts and short-term money market mutual funds.

We expect to continue to spend substantial amounts to:

- continue clinical development of plecanatide to treat GI disorders;
- continue development of other product candidates, including dolcanatide;
- finance our general and administrative expenses;
- prepare regulatory approval applications and seek approvals for plecanatide and other product candidates, including dolcanatide;

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- license or acquire additional technologies;
- manufacture product for clinical trials;
- launch and commercialize our product candidates, if any such product candidates receive regulatory approval; and
- develop and implement sales, marketing and distribution capabilities.

We will need to raise additional capital to fund our future operations and we cannot be certain that funding will be available on acceptable terms on a timely basis, or at all. To the extent that we raise additional funds by issuing equity securities, our stockholders may experience significant dilution. Any debt financing, if available, may involve restrictive covenants that impact our ability to conduct our business. If we are unable to raise additional capital when required or on acceptable terms, we may have to significantly delay, scale back or discontinue the development and/or commercialization of our lead product candidates. We also may be required to:

- seek collaborators for our product candidates at an earlier stage than otherwise would be desirable and on terms that are less favorable than might otherwise be available; and/or
- relinquish license or otherwise dispose of rights to technologies, product candidates or products that we would otherwise seek to develop or commercialize ourselves on unfavorable terms.

We do not have any products that are approved for commercial sale and therefore do not expect to generate any revenues from product sales in the foreseeable future, if ever.

We currently do not have any products that are approved for commercial sale. To date, we have funded our operations primarily from sales of our equity and debt securities. We have not received, and do not expect to receive for at least the next several years, if at all, any revenues from the commercialization of our product candidates. To obtain revenues from sales of our product candidates, we must succeed, either alone or with third parties, in developing, obtaining regulatory approval for, manufacturing and marketing drugs with commercial potential. We may never succeed in these activities, and may not generate sufficient revenues to continue our business operations or achieve profitability.

We have incurred significant losses since inception and anticipate that we will incur continued losses for the foreseeable future.

As of March 31, 2015, we had an accumulated deficit of approximately \$294 million. We expect to incur significant and increasing operating losses for the next several years as we expand our research and development, continue our clinical trials of plecanatide for the treatment of GI disorders, acquire or license technologies, advance other product candidates into clinical development, including dolcanatide, complete clinical trials, seek regulatory approval and, if we receive FDA approval, commercialize our products. Because of the numerous risks and uncertainties associated with product development efforts, we are unable to predict the extent of any future losses or when we will become profitable, if at all. If we are unable to achieve and then maintain profitability, the market value of our common stock will likely experience significant decline.

We are largely dependent on the success of our lead product candidate, plecanatide, and we cannot be certain that this product candidate will receive regulatory approval or be successfully commercialized.

We currently have no products for sale, and we cannot guarantee that we will ever have any drug products approved for sale. We and our product candidates are subject to extensive regulation by the FDA and comparable regulatory authorities in other countries governing, among other things, research, testing, clinical trials, manufacturing, labeling, promotion, selling, adverse event reporting and recordkeeping. We are not permitted to market any of our product candidates in or outside the United States until we receive approval of a new drug application, or NDA, for a product candidate from the FDA or the equivalent approval from a foreign regulatory authority. Obtaining FDA approval is a lengthy, expensive and uncertain process. We currently have one lead product candidate, plecanatide for the treatment of GI disorders, and the success of our business currently depends on our successful development, approval and commercialization. This product candidate has not completed the clinical development process; therefore, we have not yet submitted an NDA or foreign equivalent, or received marketing approval for this product candidate anywhere in the world.

The clinical development program for plecanatide may not lead to commercial products for a number of reasons, including if we fail to obtain necessary approvals from the FDA or foreign regulatory authorities because our clinical trials fail to demonstrate to their satisfaction that this product candidate is safe and effective. We may also fail to obtain the necessary approvals if we have inadequate financial or other resources to advance our product candidates through the clinical trial process. Any failure or delay in completing clinical trials or obtaining regulatory approval for plecanatide in a timely manner would have a material adverse impact on our business and our stock price.

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We will need to obtain FDA approval of any proposed product brand names, and any failure or delay associated with such approval may adversely impact our business.

A pharmaceutical product cannot be marketed in the U.S. or other countries until it has completed a rigorous and extensive regulatory review processes, including approval of a brand name. Any brand names we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the U.S. Patent and Trademark Office, or the PTO. The FDA typically conducts a review of proposed product brand names, including an evaluation of potential for confusion with other product names. The FDA may also object to a product brand name if we believe the name inappropriately implies medical claims. If the FDA objects to any of our proposed product brand names, we may be required to adopt an alternative brand name for our product candidates. If we adopt an alternative brand name, we would lose the benefit of our existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product brand name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to commercialize our product candidates.

Clinical trials involve a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Our product candidates may not prove to be safe and efficacious in clinical trials and may not meet all the applicable regulatory requirements needed to receive regulatory approval. In order to receive regulatory approval for the commercialization of our product candidates, we must conduct, at our own expense, extensive preclinical testing and clinical trials to demonstrate safety and efficacy of these product candidates for the intended indication of use. Clinical testing is expensive, can take many years to complete, if at all, and its outcome is uncertain. Failure can occur at any time during the clinical trial process.

The results of preclinical studies and early clinical trials of new drugs do not necessarily predict the results of later-stage clinical trials. The design of our clinical trials is based on many assumptions about the expected effects of our product candidates, and if those assumptions are incorrect may not produce statistically significant results. Preliminary results may not be confirmed on full analysis of the detailed results of an early clinical trial. Product candidates in later stages of clinical trials may fail to show safety and efficacy sufficient to support intended use claims despite having progressed through initial clinical testing. The data collected from clinical trials of our product candidates may not be sufficient to support the filing of an NDA or to obtain regulatory approval in the United States or elsewhere. Because of the uncertainties associated with drug development and regulatory approval, we cannot determine if or when we will have an approved product for commercialization or achieve sales or profits.

Delays in clinical testing could result in increased costs to us and delay our ability to generate revenue.

We may experience delays in clinical testing of our product candidates. We do not know whether planned clinical trials will begin on time, will need to be redesigned or will be completed on schedule, if at all. Clinical trials can be delayed for a variety of reasons, including delays in obtaining regulatory approval to commence a clinical trial, in securing clinical trial agreements with prospective sites with acceptable terms, in obtaining institutional review board approval to conduct a clinical trial at a prospective site, in recruiting patients to participate in a clinical trial or in obtaining sufficient supplies of clinical trial materials. Many factors affect patient enrollment, including the size of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the clinical trial, competing clinical trials and new drugs approved for the conditions we are investigating. Clinical investigators will need to decide whether to offer their patients enrollment in clinical trials of our product candidates versus treating these patients with commercially available drugs that have established safety and efficacy profiles. Any

delays in completing our clinical trials will increase our costs, slow down our product development and timeliness and approval process and delay our ability to generate revenue.

The FDA's expectations for clinical trials may change over time, complicating the process of obtaining evidence to support approval of our product candidates.

In May 2012, the FDA's Center for Drugs Evaluation and Research, or CDER, released guidance entitled: Irritable Bowel Syndrome Clinical Evaluation of Products for Treatment to assist the product sponsors developing new drugs for the treatment of IBS. In pertinent part, this document provides recommendations for IBS clinical trial design and endpoints, and describes the need for the future development of patient-reported outcome, or PRO, instruments for use in IBS clinical trials. The clinical trials we have planned for plecanatide are designed to follow the recommendations included in this guidance. The guidance document represents the FDA's thinking on the clinical evaluation of products for the treatment of IBS. FDA guidance documents, however, do not establish legally enforceable requirements, should be viewed only as recommendations, and may be changed at any time. Therefore, even insofar as we intend to follow the recommendations provided in the guidance document, we cannot be sure that the FDA will accept the results of our clinical research even if such research follows the recommendations in the guidance document.

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We may be required to suspend or discontinue clinical trials due to unexpected side effects or other safety risks that could preclude approval of our product candidates.

Our clinical trials may be suspended at any time for a number of reasons. For example, we may voluntarily suspend or terminate our clinical trials if at any time we believe that they present an unacceptable risk to the clinical trial patients. In addition, the FDA or other regulatory agencies may order the temporary or permanent discontinuation of our clinical trials at any time if they believe that the clinical trials are not being conducted in accordance with applicable regulatory requirements or that they present an unacceptable safety risk to the clinical trial patients.

Administering any product candidate to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our product candidates and could result in the FDA or other regulatory authorities denying further development or approval of our product candidates for any or all targeted indications. Ultimately, some or all of our product candidates may prove to be unsafe for human use. Moreover, we could be subject to significant liability if any volunteer or patient suffers, or appears to suffer, adverse health effects as a result of participating in our clinical trials.

If we fail to comply with healthcare regulations, we could face substantial enforcement actions, including civil and criminal penalties and our business, operations and financial condition could be adversely affected.

As a developer of pharmaceuticals, even though we do not intend to make referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse, false claims and patients privacy rights are and will be applicable to our business. We could be subject to healthcare fraud and abuse laws and patient privacy laws of both the federal government and the states in which we conduct our business.

The laws include:

- the federal healthcare program anti-kickback law, which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;
- federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent, and which may apply to entities like us which provide coding and billing information to customers;

- the federal Health Insurance Portability and Accountability Act of 1996, which prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters and which also imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information;
- the Federal Food, Drug, and Cosmetic Act, which among other things, strictly regulates drug manufacturing and product marketing, prohibits manufacturers from marketing drug products for off-label use and regulates the distribution of drug samples; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by federal laws, thus complicating compliance efforts.

If our operations are found to be in violation of any of the laws described above or any governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security and fraud laws may prove costly.

If we are unable to satisfy regulatory requirements, we may not be able to commercialize our product candidates.

We need FDA approval prior to marketing our product candidates in the United States. If we fail to obtain FDA approval to market our product candidates, we will be unable to sell our product candidates in the United States and we will not generate any revenue.

The FDA's review and approval process, including among other things, evaluation of preclinical studies and clinical trials of a product candidate as well as the manufacturing process and facility, is lengthy, expensive and uncertain. To receive approval, we must, among other things, demonstrate with substantial evidence from well-designed and well-controlled pre-clinical testing and clinical trials that the product candidate is both safe and effective for each indication for which approval is sought. Satisfaction of

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these requirements typically takes several years and the time needed to satisfy them may vary substantially, based on the type, complexity and novelty of the pharmaceutical product. We cannot predict if or when we will submit an NDA for approval for any of our product candidates currently under development. Any approvals we may obtain may not cover all of the clinical indications for which we are seeking approval or may contain significant limitations on the conditions of use.

The FDA has substantial discretion in the NDA review process and may either refuse to file our NDA for substantive review or may decide that our data is insufficient to support approval of our product candidates for the claimed intended uses. Following any regulatory approval of our product candidates, we will be subject to continuing regulatory obligations such as safety reporting, required and additional post marketing obligations, and regulatory oversight of promotion and marketing. Even if we receive regulatory approvals, the FDA may subsequently seek to withdraw approval of our NDA if we determine that new data or a reevaluation of existing data show the product is unsafe for use under the conditions of use upon the basis of which the NDA was approved, or based on new evidence of adverse effects or adverse clinical experience, or upon other new information. If the FDA does not file or approve our NDA or withdraws approval of our NDA, the FDA may require that we conduct additional clinical trials, preclinical or manufacturing studies and submit that data before it will reconsider our application. Depending on the extent of these or any other requested studies, approval of any applications that we submit may be delayed by several years, may require us to expend more resources than we have available, or may never be obtained at all.

We will also be subject to a wide variety of foreign regulations governing the development, manufacture and marketing of our products. Whether or not FDA approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries must still be obtained prior to marketing the product in those countries. The approval process varies and the time needed to secure approval in any region such as the European Union or in a country with an independent review procedure may be longer or shorter than that required for FDA approval. We cannot assure you that clinical trials conducted in one country will be accepted by other countries or that an approval in one country or region will result in approval elsewhere.

If our product candidates are unable to compete effectively with marketed drugs targeting similar indications as our product candidates, our commercial opportunity will be reduced or eliminated.

We face competition generally from established pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Small or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize GI drugs that are safer, more effective, have fewer side effects or are less expensive than our product candidates. These potential competitors compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient enrollment for clinical trials, as well as in acquiring technologies and technology licenses complementary to our programs or advantageous to our business.

If approved and commercialized, plecanatide will compete with at least two currently approved prescription therapies for the treatment of CC and IBS-C, Amitiza and Linzess. In addition, over-the-counter products are also used to treat certain symptoms of CC and IBS-C. We believe other companies are developing products that will compete with plecanatide should they be approved by the FDA. To our knowledge, other potential competitors are in earlier stages of development. If potential competitors are successful in completing drug development for their product candidates and obtain approval from the FDA, they could limit the demand for plecanatide. We expect that our ability to compete effectively will depend upon our ability to:

- successfully and rapidly complete clinical trials and submit for and obtain all requisite regulatory approvals in a cost-effective manner;
- maintain a proprietary position for our products and manufacturing processes and other related product technology;
- attract and retain key personnel;
- develop relationships with physicians prescribing these products; and
- build an adequate sales and marketing infrastructure for our product candidates.

Because we will be competing against significantly larger companies with established track records, we will have to demonstrate that, based on experience, clinical data, side-effect profiles and other factors, our products, if approved, are competitive with other products. If we are unable to compete effectively in the GI drug market and differentiate our products from other marketed GI drugs, we may never generate meaningful revenue.

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If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our product candidates, conduct our clinical trials and commercialize our product candidates.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel and on our ability to develop and maintain important relationships with leading academic institutions, clinicians and scientists. We are highly dependent upon our senior management and scientific staff, particularly Gary S. Jacob, Ph.D., our President and Chief Executive Officer and Kunwar Shailubhai, Ph.D., our Chief Scientific Officer. The loss of services of Dr. Jacob or one or more of our other members of senior management could delay or prevent the successful completion of our planned clinical trials or the commercialization of our product candidates.

The competition for qualified personnel in the biotechnology and pharmaceuticals field is intense. We will need to hire additional personnel as we expand our clinical development and commercial activities. We may not be able to attract and retain quality personnel on acceptable terms given the competition for such personnel among biotechnology, pharmaceutical and other companies.

We will need to increase the size of our organization, and we may experience difficulties in managing growth.

We are a small company with 37 employees as of June 30, 2015. To continue our clinical trials and commercialize our product candidates, we will need to expand our employee base for managerial, operational, financial and other resources. Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. Over the next 12 months depending on the progress of our planned clinical trials, we plan to add additional employees to assist us with our clinical and commercial programs. Our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to:

- manage development efforts effectively;
- manage our clinical trials effectively;
- integrate additional management, administrative, manufacturing and sales and marketing personnel;
- maintain sufficient administrative, accounting and management information systems and controls; and
- hire and train additional qualified personnel.

We may not be able to accomplish these tasks, and our failure to accomplish any of them could harm our financial results and impact our ability to achieve development milestones.

We currently have no sales and marketing organization. If we are unable to establish a direct sales force in the United States to promote our products, the commercial opportunity for our products may be diminished.

We currently have no sales and marketing organization. If any of our product candidates are approved by the FDA, we may market that product through our own sales force. We will incur significant additional expenses and commit significant additional management resources to establish our own sales force. We may not be able to establish these capabilities despite these additional expenditures. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire and train sales and marketing personnel. If we elect to rely on third parties to sell our product candidates in the United States, we may receive less revenue than if we sold our products directly. In addition, although we would intend to use due diligence in monitoring their activities, we may have little or no control over the sales efforts of those third parties. In the event we are unable to develop our own sales force or collaborate with a third party to sell our product candidates, we may not be able to commercialize our product candidates which would negatively impact our ability to generate revenue.

We may need to rely on third parties to market and commercialize our product candidates in international markets.

Currently, we do not have any plans to enter international markets. In the future, if appropriate regulatory approvals are obtained, we may commercialize our product candidates in international markets. However, we have not decided how to commercialize our product candidates in those markets. We may decide to build our own sales force or sell our products through third parties. If we decide to sell our product candidates in international markets through a third party, we may not be able to enter into any marketing arrangements on favorable terms or at all. In addition, these arrangements could result in lower levels of income to us than if we marketed our product candidates entirely on our own. If we are unable to enter into a marketing arrangement for our product candidates in international markets, we may not be able to develop an effective international sales force to successfully commercialize those products in international markets. If we fail to enter into marketing arrangements for our products and are unable to develop an effective international sales force, our ability to generate revenue would be limited.

If the manufacturers upon whom we rely fail to produce plecanatide and our other product candidates, including dolcanatide, in the volumes that we require on a timely basis, or fail to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of our product candidates.

We do not currently possess internal manufacturing capacity. We currently utilize the services of contract manufacturers to manufacture our clinical supplies. With respect to the manufacturing of plecanatide, we have executed supply agreements with two contract manufacturers sufficient to meet our foreseeable clinical trial requirements. Any curtailment in the availability of plecanatide, however, could result in production or other delays with consequent adverse effects on us. In addition, because regulatory authorities

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must generally approve raw material sources for pharmaceutical products, changes in raw material suppliers may result in production delays or higher raw material costs.

We continue to pursue additional active pharmaceutical ingredients, or API, and drug product supply agreements with other manufacturers. We may be required to agree to minimum volume requirements, exclusivity arrangements or other restrictions with the contract manufacturers. We may not be able to enter into long-term agreements on commercially reasonable terms, or at all. If we change or add manufacturers, the FDA and comparable foreign regulators may require approval of the changes. Approval of these changes could require new testing by the manufacturer and compliance inspections to ensure the manufacturer is conforming to all applicable laws and regulations, including good manufacturing practices, or GMP. In addition, the new manufacturers would have to be educated in or independently develop the processes necessary for the production of our product candidates. Peptide manufacturing is a highly specialized manufacturing business. While we believe we will have long term arrangements with a sufficient number of contract manufacturers, if we lose a manufacturer, it would take us a substantial amount of time to identify and develop a relationship, and seek regulatory approval, where necessary, for an alternative manufacturer.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products may encounter difficulties in production, particularly in scaling up production. These problems include difficulties with production costs and yields, quality control, including stability of the product and quality assurance testing, shortages of qualified personnel, as well as compliance with federal, state and foreign regulations. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of our clinical trials, increase the costs associated with conducting our clinical trials and, depending upon the period of delay, require us to commence new clinical trials at significant additional expense or to terminate a clinical trial.

We are responsible for ensuring that each of our contract manufacturers comply with the GMP requirements of the FDA and other regulatory authorities from which we seek to obtain product approval. These requirements include, among other things, quality control, quality assurance and the maintenance of records and documentation. The approval process for NDAs includes a review of the manufacturer's compliance with GMP requirements. We are responsible for regularly assessing a contract manufacturer's compliance with GMP requirements through record reviews and periodic audits and for ensuring that the contract manufacturer takes responsibility and corrective action for any identified deviations. Manufacturers of plecanatide and other product candidates, including dolcanatide, may be unable to comply with these GMP requirements and with other FDA and foreign regulatory requirements, if any.

While we will oversee compliance by our contract manufacturers, ultimately we will not have control over our manufacturers' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval. If the safety of plecanatide or other product candidates is compromised due to a manufacturer's failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize plecanatide or other product candidates, and we may be held liable for any injuries sustained as a result. Any of these factors could cause a delay of clinical trials, regulatory submissions, approvals or commercialization of plecanatide or other product candidates, entail higher costs or result in us being unable to effectively commercialize plecanatide or other product candidates. Furthermore, if our manufacturers fail to deliver the required commercial quantities on a timely basis and at commercially reasonable prices, we may be unable to meet demand for any approved products and would lose potential revenues.

We may not be able to manufacture our product candidates in commercial quantities, which would prevent us from commercializing our product candidates.

To date, our product candidates have been manufactured in small quantities for preclinical studies and clinical trials. If any of our product candidates is approved by the FDA or comparable regulatory authorities in other countries for commercial sale, we will need to manufacture such product candidate in larger quantities. We may not be able to increase successfully the manufacturing capacity for any of our product candidates in a timely or economic manner, or at all. Significant scale-up of manufacturing may require additional validation studies, which the FDA must review and approve. If we are unable to increase successfully the manufacturing capacity for a product candidate, the clinical trials as well as the regulatory approval or commercial launch of that product candidate may be delayed or there may be a shortage in supply. Our product candidates require precise, high quality manufacturing. Our failure to achieve and maintain these high quality manufacturing standards in collaboration with our third-party manufacturers, including the incidence of manufacturing errors, could result in patient injury or death, product recalls or withdrawals, delays or failures in product testing or delivery, cost overruns or other problems that could harm our business, financial condition and results of operations.

Materials necessary to manufacture our product candidates may not be available on commercially reasonable terms, or at all, which may delay the development and commercialization of our product candidates.

We rely on the third-party manufacturers of our product candidates to purchase from third-party suppliers the materials necessary to produce the bulk APIs and product candidates for our clinical trials, and we will rely on such manufacturers to purchase such materials to produce the APIs and finished products for any commercial distribution of our products if we obtain marketing approval. Suppliers may not sell these materials to our manufacturers at the time they need them in order to meet our required delivery schedule or on commercially reasonable terms, if at all. We do not have any control over the process or timing of the acquisition of these

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materials by our manufacturers. Moreover, we currently do not have any agreements for the production of these materials. If our manufacturers are unable to obtain these materials for our clinical trials, testing of the affected product candidate would be delayed, which may significantly impact our ability to develop the product candidate. If we, or our manufacturers, are unable to purchase these materials after regulatory approval has been obtained for one of our products, the commercial launch of such product would be delayed or there would be a shortage in supply of such product, which would harm our ability to generate revenues from such product and achieve or sustain profitability.

Our product candidates, if approved for sale, may not gain acceptance among physicians, patients and the medical community, thereby limiting our potential to generate revenues.

If one of our product candidates is approved for commercial sale by the FDA or other regulatory authorities, the degree of market acceptance of any approved product by physicians, healthcare professionals and third-party payors and our profitability and growth will depend on a number of factors, including:

- demonstration of safety and efficacy;
- changes in the practice guidelines and the standard of care for the targeted indication;
- relative convenience and ease of administration;
- the prevalence and severity of any adverse side effects;
- budget impact of adoption of our product on relevant drug formularies
- the availability, cost and potential advantages of alternative treatments, including less expensive generic drugs;
- pricing, reimbursement and cost effectiveness, which may be subject to regulatory control;
- effectiveness of our or any of our partners' sales and marketing strategies;
- the product labeling or product insert required by the FDA or regulatory authority in other countries; and
- the availability of adequate third-party insurance coverage or reimbursement.

If any product candidate that we develop does not provide a treatment regimen that is as beneficial as, or is perceived as being as beneficial as, the current standard of care or otherwise does not provide patient benefit, that product candidate, if approved for commercial sale by the FDA or other regulatory authorities, likely will not achieve market acceptance. Our ability to effectively promote and sell any approved products will also depend on pricing and cost-effectiveness, including our ability to produce a product at a competitive price and our ability to obtain sufficient third-party coverage or reimbursement. If any product candidate is approved but does not achieve an adequate level of acceptance by physicians, patients and third-party payors, our ability to generate revenues from that product would be substantially reduced. In addition, our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources, may be constrained by FDA rules and policies on product promotion, and may never be successful.

Guidelines and recommendations published by various organizations can impact the use of our products candidates.

Government agencies promulgate regulations and guidelines directly applicable to us and to our product candidates. In addition, professional societies, practice management groups, private health and science foundations and organizations involved in various diseases from time to time may also publish guidelines or recommendations to the health care and patient communities. Recommendations of government agencies or these other groups or organizations may relate to such matters as usage, dosage, route of administration and use of concomitant therapies. Recommendations or guidelines suggesting the reduced use of our product candidates or the use of competitive or alternative products that are followed by patients and health care providers could result in decreased use of our proposed product candidates.

If product liability lawsuits are successfully brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability lawsuits related to the testing of our product candidates, and will face an even greater risk if we sell our product candidates commercially. Currently, we are not aware of any anticipated product liability claims with respect to our product candidates. In the future, an individual may bring a liability claim against us if one of our product candidates causes, or merely appears to have caused, an injury. If we cannot successfully defend ourselves against the product liability claim, we may incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for our product candidates;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs of related litigation;
- initiation of investigations by regulators;
- substantial monetary awards to patients or other claimants;
- distraction of management's attention from our primary business;
- product recalls;

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- loss of revenue; and
- the inability to commercialize our product candidates.

We have clinical trial liability insurance with a \$5,000,000 aggregate limit. We intend to expand our insurance coverage to include the sale of commercial products if marketing approval is obtained for our product candidates. Our current insurance coverage may prove insufficient to cover any liability claims brought against us. In addition, because of the increasing costs of insurance coverage, we may not be able to maintain insurance coverage at a reasonable cost or obtain insurance coverage that will be adequate to satisfy liabilities that may arise.

Our failure to successfully discover, acquire, develop and market additional product candidates or approved products could impair our ability to grow.

As part of our growth strategy, we intend to develop and market additional products and product candidates. We are pursuing various therapeutic opportunities through our pipeline. We may spend several years completing our development of any particular current or future internal product candidate, and failure can occur at any stage. The product candidates to which we allocate our resources may not end up being successful. In addition, because our internal research capabilities are limited, we may be dependent upon pharmaceutical and biotechnology companies, academic scientists and other researchers to sell or license products or technology to us. The success of this strategy depends partly upon our ability to identify, select, discover and acquire promising pharmaceutical product candidates and products. Failure of this strategy would impair our ability to grow.

The process of proposing, negotiating and implementing a license or acquisition of a product candidate or approved product is lengthy and complex. Other companies, including some with substantially greater financial, marketing and sales resources, may compete with us for the license or acquisition of product candidates and approved products. We have limited resources to identify and execute the acquisition or in-licensing of third-party products, businesses and technologies and integrate them into our current infrastructure. Moreover, we may devote resources to potential acquisitions or in-licensing opportunities that are never completed, or we may fail to realize the anticipated benefits of such efforts. We may not be able to acquire the rights to additional product candidates on terms that we find acceptable, or at all. In addition, future acquisitions may entail numerous operational and financial risks, including:

- disruption of our business and diversion of our management's time and attention to develop acquired products or technologies;
- incurrence of substantial debt, dilutive issuances of securities or depletion of cash to pay for acquisitions;
- higher than expected acquisition and integration costs;
- difficulty in combining the operations and personnel of any acquired businesses with our operations and personnel;
- increased amortization expenses;
- assumption of known and unknown liabilities;

- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to motivate key employees of any acquired businesses.

Further, any product candidate that we acquire may require additional development efforts prior to commercial sale, including extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All product candidates are prone to risks of failure typical of pharmaceutical product development, including the possibility that a product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities.

Even if our product candidates receive regulatory approval, they may still face future development and regulatory difficulties.

Even if U.S. regulatory approval is obtained, the FDA may still impose significant restrictions on a product's indicated uses or impose ongoing requirements for potentially costly post-approval studies. Plecanatide and our other product candidates, including dolcanatide, would also be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and submission of safety and other post-market information. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with GMP, regulations. If we or a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product or the manufacturer, including requiring withdrawal of the product from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning letters;
- impose civil or criminal penalties;
- suspend regulatory approval;
- suspend any ongoing clinical trials;

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- refuse to approve pending applications or supplements to applications filed by us;
- impose restrictions on operations, including costly new manufacturing requirements;
- seize or detain products or request us to initiate a product recall; or
- pursue and obtain an injunction.

Drugs approved to treat IBS have been subject to considerable post-market scrutiny, with consequences up to and including voluntary withdrawal of approved products from the market. This may heighten FDA scrutiny of our product candidates before or following market approval.

Products approved for the treatment of IBS have been subject to considerable post-market scrutiny. For example, in 2007, Novartis voluntarily discontinued marketing Zelnorm (tegaserod), a product approved for the treatment of women with IBS-C, after the FDA found an increased risk of serious cardiovascular events associated with the use of the drug. Earlier, in 2000, GlaxoWellcome withdrew Lotronex (alosetron), which was approved for women with severe diarrhea-prominent IBS, after the manufacturer received numerous reports of adverse events or AEs, including ischemic colitis, severely obstructed or ruptured bowel, or death. In 2002, the FDA approved the manufacturer's application to make Lotronex available again, on the condition that the drug only be made available through a restricted marketing program.

Although plecanatide is being investigated for IBS, plecanatide is from a different pharmacologic class than Zelnorm or Lotronex, and would not be expected to share the same clinical risk profile as those agents. Nevertheless, because these products are in the same or related therapeutic classes, it is possible that the FDA will have heightened scrutiny of plecanatide or any other agent under development for IBS. This could delay product approval, increase the cost of our clinical development program, or increase the cost of post-market study commitments for our IBS product candidates, including plecanatide.

Even if our product candidates receive regulatory approval in the United States, we may never receive approval to commercialize them outside of the United States.

In the future, we may seek to commercialize plecanatide and/or our other product candidates, including dolcanatide, in foreign countries outside of the United States. In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other jurisdictions regarding safety and efficacy. Approvals procedures vary among jurisdictions and can involve product testing and administrative review periods different from, and greater than, those in the United States. The time required to obtain approval in other jurisdictions might differ from that required to obtain FDA approval. The regulatory approval process in other jurisdictions may include all of the risks detailed above regarding FDA approval in the United States as well as other risks. Regulatory approval in one jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory processes in others. Failure to obtain regulatory approvals in other jurisdictions or any delay or setback in obtaining such approvals could have the same adverse effects detailed above regarding FDA approval in the United States. As described above, such effects include the risks that plecanatide or our other product candidates may not be approved for all indications for use included in proposed labeling or for any indications at all, which could limit the uses of plecanatide or other product candidates and have an adverse effect on our products' commercial potential or require costly post-marketing studies.

We rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to seek or obtain regulatory approval for or commercialize our product candidates.

We have agreements with third-party contract research organizations, or CROs, under which we have delegated to the CROs the responsibility to coordinate and monitor the conduct of our clinical trials and to manage data for our clinical programs. We, our CROs and our clinical sites are required to comply with current Good Clinical Practices, or cGCPs, regulations and guidelines issued by the FDA and by similar governmental authorities in other countries where we are conducting clinical trials. We have an ongoing obligation to monitor the activities conducted by our CROs and at our clinical sites to confirm compliance with these requirements. In the future, if we, our CROs or our clinical sites fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our marketing applications. In addition, our clinical trials must be conducted with product produced under cGMP regulations, and will require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to their failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed.

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Reimbursement may not be available for our product candidates, which would impede sales.

Market acceptance and sales of our product candidates may depend on coverage and reimbursement policies and health care reform measures. Decisions about formulary coverage as well as levels at which government authorities and third-party payers, such as private health insurers and health maintenance organizations, reimburse patients for the price they pay for our products as well as levels at which these payors pay directly for our products, where applicable, could affect whether we are able to commercialize these products. We cannot be sure that reimbursement will be available for any of these products. Also, we cannot be sure that coverage or reimbursement amounts will not reduce the demand for, or the price of, our products. We have not commenced efforts to have our product candidates reimbursed by government or third party payors. If coverage and reimbursement are not available or are available only at limited levels, we may not be able to commercialize our products.

In recent years, officials have made numerous proposals to change the health care system in the United States. These proposals include measures that would limit or prohibit payments for certain medical treatments or subject the pricing of drugs to government control. In addition, in many foreign countries, particularly the countries of the European Union, the pricing of prescription drugs is subject to government control. If our products are or become subject to government regulation that limits or prohibits payment for our products, or that subjects the price of our products to governmental control, we may not be able to generate revenue, attain profitability or commercialize our products.

As a result of legislative proposals and the trend towards managed health care in the United States, third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. They may also impose strict prior authorization requirements and/or refuse to provide any coverage of uses of approved products for medical indications other than those for which the FDA has granted market approvals. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse patients for their use of newly-approved drugs, which in turn will put pressure on the pricing of drugs.

Healthcare reform measures could hinder or prevent our product candidates' commercial success.

The U.S. government and other governments have shown significant interest in pursuing healthcare reform. Any government-adopted reform measures could adversely impact the pricing of healthcare products and services in the United States or internationally and the amount of reimbursement available from governmental agencies or other third party payors. The continuing efforts of the U.S. and foreign governments, insurance companies, managed care organizations and other payors of health care services to contain or reduce health care costs may adversely affect our ability to set prices for our products which we believe are fair, and our ability to generate revenues and achieve and maintain profitability.

New laws, regulations and judicial decisions, or new interpretations of existing laws, regulations and decisions, that relate to healthcare availability, methods of delivery or payment for products and services, or sales, marketing or pricing, may limit our potential revenue, and we may need to revise our research and development programs. The pricing and reimbursement environment may change in the future and become more challenging due to several reasons, including policies advanced by the current executive administration in the United States, new healthcare legislation or fiscal challenges faced by government health administration authorities. Specifically, in both the United States and some foreign jurisdictions, there have been a number of legislative and regulatory proposals to change the health care system in ways that could affect our ability to sell our products profitably.

For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the PPACA has substantially changed the way healthcare is financed by both government health plans and private insurers, and significantly impacts the pharmaceutical industry. The PPACA contains a number of provisions that are expected to impact our business and operations in ways that may negatively affect our potential revenues in the future. For example, the PPACA imposes a non-deductible excise tax on pharmaceutical manufacturers or importers that sell branded prescription drugs to U.S. government programs which we believe will increase the cost of our products. In addition, as part of the PPACA's provisions closing a funding gap that currently exists in the Medicare Part D prescription drug program (commonly known as the "donut hole"), we will be required to provide a discount on branded prescription drugs equal to 50% of the government-negotiated price, for drugs provided to certain beneficiaries who fall within the donut hole. Similarly, PPACA increases the level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1% and requires collection of rebates for drugs paid by Medicaid managed care organizations. The PPACA also includes significant changes to the 340B drug discount program including expansion of the list of eligible covered entities that may purchase drugs under the program. At the same time, the expansion in eligibility for health insurance benefits created under PPACA is expected to increase the number of patients with insurance coverage who may receive our products. While it is too early to predict all the specific effects the PPACA or any future healthcare reform legislation will have on our business, they could have a material adverse effect on our business and financial condition.

Congress periodically adopts legislation like the PPACA and the Medicare Prescription Drug, Improvement and Modernization Act of 2003, that modifies Medicare reimbursement and coverage policies pertaining to prescription drugs. Implementation of these laws is subject to ongoing revision through regulatory and sub regulatory policies. Congress also may consider additional changes to Medicare policies, potentially including Medicare prescription drug policies, as part of ongoing budget negotiations. While the scope of any such legislation is uncertain at this time, there can be no assurances that future legislation or regulations will not decrease the coverage and price that we may receive for our proposed products. Other third-party payors are increasingly challenging the prices

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charged for medical products and services. It will be time consuming and expensive for us to go through the process of seeking coverage and reimbursement from Medicare and private payors. Our proposed products may not be considered cost-effective, and coverage and reimbursement may not be available or sufficient to allow us to sell our proposed products on a profitable basis. Further federal and state proposals and health care reforms are likely which could limit the prices that can be charged for the product candidates that we develop and may further limit our commercial opportunities. Our results of operations could be materially adversely affected by proposed healthcare reforms, by the Medicare prescription drug coverage legislation, by the possible effect of such current or future legislation on amounts that private insurers will pay and by other health care reforms that may be enacted or adopted in the future.

In September 2007, the Food and Drug Administration Amendments Act of 2007 was enacted, giving the FDA enhanced post-marketing authority, including the authority to require post-marketing studies and clinical trials, labeling changes based on new safety information, and compliance with risk evaluations and mitigation strategies approved by the FDA. The FDA's exercise of this authority could result in delays or increased costs during product development, clinical trials and regulatory review, increased costs to assure compliance with post-approval regulatory requirements, and potential restrictions on the sale and/or distribution of approved products.

Security breaches and other disruptions could compromise our information and expose us to liability, which would cause our business and reputation to suffer.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our suppliers and business partners, as well as personally identifiable information of clinical trial participants and employees. Similarly, our business partners and third party providers possess certain of our sensitive data. The secure maintenance of this information is critical to our operations and business strategy. Despite our security measures, our information technology and infrastructure may be vulnerable to attacks by hackers or breached due to employee error, malfeasance or other disruptions. Any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information, including our data being breached at our business partners or third-party providers, could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, disrupt our operations, and damage our reputation which could adversely affect our business.

Healthcare reform measures could hinder or prevent our product candidates' commercial success.

The U.S. government and other governments have shown significant interest in pursuing healthcare reform. Any government-adopted reform measures could adversely impact the pricing of healthcare products and services in the United States or internationally and the amount of reimbursement available from governmental agencies or other third party payors. The continuing efforts of the U.S. and foreign governments, insurance companies, managed care organizations and other payors of health care services to contain or reduce health care costs may adversely affect our ability to set prices for our products which we believe are fair, and our ability to generate revenues and achieve and maintain profitability.

New laws, regulations and judicial decisions, or new interpretations of existing laws, regulations and decisions, that relate to healthcare availability, methods of delivery or payment for products and services, or sales, marketing or pricing, may limit our potential revenue, and we may need to revise our research and development programs. The pricing and reimbursement environment may change in the future and become more challenging due to several reasons, including policies advanced by the current executive administration in the United States, new healthcare legislation or fiscal challenges faced by government health administration authorities. Specifically, in both the United States and some foreign jurisdictions, there have been a number of legislative and regulatory proposals to change the health care system in ways that could affect

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In September 2007, the Food and Drug Administration Amendments Act of 2007 was enacted, giving the FDA enhanced post-marketing authority, including the authority to require post-marketing studies and clinical trials, labeling changes based on new safety information, and compliance with risk evaluations and mitigation strategies approved by the FDA. The FDA's exercise of this authority could result in delays or increased costs during product development, clinical trials and regulatory review, increased costs to assure compliance with post-approval regulatory requirements, and potential restrictions on the sale and/or distribution of approved products.

It is difficult and costly to protect our proprietary rights, and we may not be able to ensure their protection.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of our product candidates, and the methods used to manufacture them, as well as successfully defending these patents against third-party challenges. We will only be able to protect our product candidates from unauthorized making, using, selling and offering to sell or importation by third parties to the extent that we have rights under valid and enforceable patents or trade secrets that cover these activities.

For example:

- others may be able to make compounds that are competitive with our products but that are not covered by the claims of our patents;
- we may not have been the first to make the inventions covered by our pending patent applications;
- we may not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies;
- it is possible that our pending patent applications will not result in issued patents
- it is possible that our issued patents could be narrowed in scope, invalidated, held to be unenforceable, or

circumvented;

- we may not develop additional proprietary technologies that are patentable; or
- the patents of others may have an adverse effect on our business.

We also may rely on trade secrets to protect our technology, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. While we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

We may incur substantial costs as a result of litigation or other proceedings relating to patent and other intellectual property rights and we may be unable to protect our rights to, or use, our technology.

If we choose to go to court to stop someone else from using the inventions claimed in our patents, that individual or company has the right to ask the court to rule that these patents are invalid and/or should not be enforced against that third party. These lawsuits are expensive and would consume time and other resources even if we were successful in stopping the infringement of these patents. In addition, there is a risk that the court will decide that these patents are not valid and that we do not have the right to stop the other party from using the inventions. There is also the risk that, even if the validity of these patents is upheld, the court will refuse to stop the other party on the ground that such other party's activities do not infringe our rights to these patents.

Furthermore, a third party may claim that we are using inventions covered by the third party's patent rights and may go to court to stop us from engaging in our normal operations and activities, including making or selling our product candidates. These lawsuits are costly and could affect our results of operations and divert the attention of managerial and technical personnel. There is a risk that a

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court would decide that we are infringing the third party's patents and would order us to stop the activities covered by the patents. In addition, there is a risk that a court will order us to pay the other party damages for having violated the other party's patents. The biotechnology industry has produced a proliferation of patents, and it is not always clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our products or methods of use either do not infringe the patent claims of the relevant patent and/or that the patent claims are invalid, and we may not be able to do this. Proving invalidity, in particular, is difficult since it requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents.

Because some patent applications in the United States may be maintained in secrecy until the patents are issued, patent applications in the United States and many foreign jurisdictions are typically not published until eighteen months after filing, and publications in the scientific literature often lag behind actual discoveries, we cannot be certain that others have not filed patent applications for technology covered by our issued patents or our pending applications or that we were the first to invent the technology. Our competitors have filed, and may in the future file, patent applications covering technology similar to ours. Any such patent application may have priority over our patent applications and could further require us to obtain rights to issued patents covering such technologies. If another party has filed a United States patent application on inventions similar to ours, we may have to participate in an interference proceeding declared by the PTO, to determine priority of invention in the United States. The costs of these proceedings could be substantial, and it is possible that such efforts would be unsuccessful, resulting in a loss of our United States patent position with respect to such inventions.

Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise the funds necessary to continue our operations.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submissions, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentaries, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

We have not yet registered trademarks for plecanatide in our potential markets, and failure to secure those registrations could adversely affect our ability to market our product candidate and our business.

We have not yet registered trademarks for plecanatide in any jurisdiction. Our trademark applications in the United States, when filed, and any other jurisdictions where we may file may not be allowed for registration, and our registered trademarks may not be maintained or enforced. During trademark registration proceedings, we may receive rejections. Although we are given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Failure to secure such trademark registrations in the United States and in foreign jurisdictions could adversely affect our ability to market our product candidates and our business.

Confidentiality agreements with employees and others may not adequately prevent disclosure of our trade secrets and other proprietary information and may not adequately protect our intellectual property, which could limit our ability to compete.

Because we operate in the highly technical field of research and development of small molecule drugs, we rely in part on trade secret protection in order to protect our proprietary trade secrets and unpatented know-how. However, trade secrets are difficult to protect, and we cannot be certain that others will not develop the same or similar technologies on their own. We have taken steps, including entering into confidentiality agreements with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors, to protect our trade secrets and unpatented know-how. These agreements generally require that the other party keep confidential and not disclose to third parties all confidential information developed by the party or made known to the party by us during the course of the party's relationship with us. We also typically obtain agreements from these parties that provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. Enforcing a claim that a party illegally obtained and is using our trade secrets or know-how is difficult, expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States may be less willing to protect trade secrets or know-how. The failure to obtain or maintain trade secret protection could adversely affect our competitive position.

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We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

Risks Related to the Convertible Senior Notes

The indenture for our senior convertible notes, or the Notes, contains covenants limiting our financial and operating flexibility.

The indenture for the Notes contains covenants that will restrict our ability and the ability of certain of our subsidiaries to:

- incur or guarantee additional indebtedness, other than subordinated debt;
- declare or pay any dividends on our or our subsidiaries' capital stock;
- redeem or repurchase capital stock or prepay or repurchase subordinated debt; or
- sell or license rights in North America to or otherwise encumber any of the intellectual property related to plecanatide.

These restrictive covenants could limit our ability to pursue our growth plans, restrict our flexibility in planning for, or reacting to, changes in our business and industry and increase our vulnerability to general adverse economic and industry conditions. We may enter into additional financing arrangements in the future, which could further restrict our flexibility.

Any defaults of covenants contained in the Notes may lead to an event of default under the Notes and the indenture. We may not be able to pay any amounts due to holders of the Notes in the event of such default, and such default may significantly impair our ability to satisfy our obligations under the Notes.

We will not make any adjustment to the conversion rate for Notes converted in connection with a fundamental change, and noteholders will not be compensated for any lost value of their Notes as a result of such transaction.

We will not increase or make any other adjustment to the conversion rate upon a conversion of Notes in connection with a fundamental change or similar event. Therefore, noteholders will not be compensated for any lost value of their Notes as a result of such transaction.

The Notes are effectively subordinated to any of our future secured debt and any liabilities of our subsidiaries.

The Notes will rank senior in right of payment to our future indebtedness that is expressly subordinated in right of payment to the Notes; equal in right of payment to our trade payables and other future unsecured indebtedness that is not so subordinated; effectively junior to any of our secured indebtedness to the extent of the value of the assets securing such indebtedness; and structurally junior to all future indebtedness (including trade payables) incurred by our subsidiaries. In the event of our bankruptcy, liquidation, reorganization or other winding up, our assets that secure debt ranking senior or equal in right of payment to the Notes will be available to pay obligations on the Notes only after the secured debt has been repaid in full. There may not be sufficient assets remaining to pay amounts due on any or all of the Notes then outstanding.

Servicing our debt will require a significant amount of cash, and we may not have sufficient cash flow from our business to pay our debt.

Our ability to make scheduled payments of the principal of, to pay interest on or to refinance our indebtedness, including the Notes, depends on our future performance, which is subject to economic, financial, competitive and other factors beyond our control. Our business may not generate cash flow from operations in the future sufficient to service our debt and make necessary capital expenditures. If we are unable to generate such cash flow, we may be required to adopt one or more alternatives, such as selling assets, restructuring debt or obtaining additional equity capital on terms that may be onerous or highly dilutive. Our ability to refinance our indebtedness will depend on the capital markets and our financial condition at such time. We may not be able to engage in any of these activities or engage in these activities on desirable terms, which could result in a default on our debt obligations.

Recent regulatory actions may adversely affect the trading price and liquidity of the Notes.

We expect that investors in, and potential purchasers of, the Notes may employ, or seek to employ, an arbitrage strategy with respect to the Notes. Investors that employ an arbitrage strategy with respect to the Notes typically implement that strategy by selling short the common stock underlying the Notes and dynamically adjusting their short position while they hold the Notes. Investors may also implement this hedging strategy by entering into swaps on our common stock in lieu of or in addition to short selling the common stock.

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The Securities and Exchange Commission (SEC) and other regulatory and self-regulatory authorities have implemented various rules and may adopt additional rules in the future that may impact those engaging in short selling activity involving equity securities (including our common stock), including Rule 201 of SEC regulation SHO, the Financial Industry Regulatory Authority, Inc.'s Limit Up-Limit Down program, market-wide circuit breaker systems that halt trading of stock for certain periods following specific market declines, and rules stemming from the enactment and implementation of the Dodd-Frank Wall Street Reform and Consumer Protection Act. Past regulatory actions, including emergency actions or regulations, have had a significant impact on the trading prices and liquidity of equity-linked instruments. Any governmental action that similarly restricts the ability of investors in, or potential purchasers of, the Notes to effect short sales of our common stock could similarly adversely affect the trading price and the liquidity of the Notes.

Volatility in the market price and trading volume of our common stock could adversely impact the trading price of the Notes.

The stock market in recent years has experienced significant price and volume fluctuations that have often been unrelated to the operating performance of companies. The market price of our common stock could fluctuate significantly for many reasons, including in response to the risks described in this section, elsewhere in this Annual Report on Form 10-K or the documents we have incorporated by reference in this Annual Report on Form 10-K or for reasons unrelated to our operations, such as reports by industry analysts, investor perceptions or negative announcements by our customers, competitors or suppliers regarding their own performance, as well as industry conditions and general financial, economic and political instability. A decrease in the market price of our common stock would likely adversely impact the trading price of the Notes. The market price of our common stock could also be affected by possible sales of our common stock by investors who view the Notes as a more attractive means of equity participation in us and by hedging or arbitrage trading activity that we expect to develop involving our common stock. This trading activity could, in turn, affect the trading prices of the Notes. This may result in greater volatility in the trading price of the Notes than would be expected for non-convertible debt securities.

Subject to certain limitations, we continue to have the ability to incur debt; if we incur substantial additional debt, these higher levels of debt may affect our ability to pay the principal of and interest on the Notes.

Subject to certain limitations, we and our subsidiaries may be able to incur substantial additional debt in the future, some of which may be secured debt. The indenture governing the Notes does not restrict our ability to incur additional subordinated indebtedness or require us to maintain financial ratios or specified levels of net worth or liquidity. If we incur substantial additional indebtedness in the future, these higher levels of indebtedness may affect our ability to pay the principal of and interest on the Notes, or any fundamental change purchase price, and our creditworthiness generally.

We may not have the ability to raise the funds necessary to purchase the Notes as required upon a fundamental change, and our future debt may contain limitations on our ability to purchase of the Notes.

Following a fundamental change as defined, holders of Notes will have the right to require us to purchase their Notes for cash. A fundamental change may also constitute an event of default or prepayment under, and result in the acceleration of the maturity of, our then-existing indebtedness. We cannot assure noteholders that we will have sufficient financial resources, or will be able to arrange financing, to pay the fundamental change purchase price in cash with respect to any Notes surrendered by holders for purchase upon a fundamental change. In addition, restrictions in our then existing credit facilities or other indebtedness, if any, may not allow us to purchase the Notes upon a fundamental change. Our failure to purchase the Notes upon a fundamental change when required would result in an event of default with respect to the Notes which could, in turn, constitute a default under the terms of our other indebtedness, if any. If the repayment of the related indebtedness were to be accelerated after any applicable notice or grace periods, we may not have sufficient funds to repay the indebtedness and

purchase the Notes.

Some significant restructuring transactions may not constitute a fundamental change, in which case we would not be obligated to offer to purchase the Notes.

Upon the occurrence of a fundamental change as defined, noteholders have the right to require us to purchase their Notes. However, the fundamental change provisions will not afford protection to holders of Notes in the event of certain transactions that could adversely affect the Notes. For example, transactions such as leveraged recapitalizations, refinancings, restructurings or acquisitions initiated by us would not constitute a fundamental change requiring us to repurchase the Notes. In addition, holders will not be entitled to require us to purchase their Notes upon a significant change in the composition of our board. In the event of any such transaction, holders of the Notes would not have the right to require us to purchase their Notes, even though each of these transactions could increase the amount of our indebtedness, or otherwise adversely affect our capital structure or any credit ratings, thereby adversely affecting holders of the Notes.

Future sales of our common stock in the public market could lower the market price for our common stock and adversely impact the trading price of the Notes.

In the future, we may sell additional shares of our common stock to raise capital. In addition, a substantial number of shares of our common stock are reserved for issuance upon the exercise of stock options and warrants and upon conversion of the Notes. We

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cannot predict the size of future issuances or the effect, if any, that they may have on the market price for our common stock. The issuance and sale of substantial amounts of common stock, or the perception that such issuances and sales may occur, could adversely affect the trading price of the Notes and the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities.

The Notes may not have an active market, and the price may be volatile, so noteholders may be unable to sell their Notes at the price they desire or at all.

The Notes are a new issue of securities for which there is currently no active trading market. We cannot be certain that a liquid market will develop for the Notes, that noteholders will be able to sell any of the Notes at a particular time (if at all) or that the prices they receive if or when noteholders sell the Notes will be above their initial offering price. In addition, we do not intend to apply to list the Notes on any securities exchange or for inclusion of the Notes on any automated dealer quotation system. The initial purchasers have advised us that they intend to make a market in the Notes, but they are not obligated to do so and may discontinue any market-making in the Notes at any time in their sole discretion and without notice. Future trading prices of the Notes on any market that may develop will depend on many factors, including our operating performance and financial condition, prevailing interest rates, the market for similar securities and general economic conditions.

Moreover, even if noteholders are able to sell their Notes, they may not receive a favorable price for their Notes. Future trading prices of the Notes will depend on many factors, including, among other things, prevailing interest rates, our operating results, the price of our common stock and the market for similar securities. Historically, the market for convertible debt has been subject to disruptions that have caused volatility in prices. It is possible that the market for the Notes will be subject to disruptions that may have a negative effect on the holders of the Notes, regardless of our prospects or financial performance.

Any adverse rating of the Notes may negatively affect the trading price and liquidity of the Notes and the price of our common stock.

We do not intend to seek a rating on the Notes. However, if a rating service were to rate the Notes and if such rating service were to assign the Notes a rating lower than the rating expected by investors or were to lower its rating on the Notes below the rating initially assigned to the Notes or otherwise announce its intention to put the Notes on credit watch, the trading price or liquidity of the Notes and the price of our common stock could decline.

The conversion rate of the Notes may not be adjusted for all dilutive events.

The conversion rate of the Notes is subject to adjustment for certain events, including, but not limited to, the issuance to all or substantially all holders of our common stock of stock dividends, certain rights, options or warrants, capital stock, indebtedness, assets or cash, and subdivisions and combinations of our common stock, and certain issuer tender or exchange offers as defined. However, the conversion rate will not be adjusted for other events, such as a third-party tender or exchange offer or an issuance of common stock for cash, that may adversely affect the trading price of the Notes or the common stock. An event that adversely affects the value of the Notes may occur, and that event may not result in an adjustment to the conversion rate.

The Notes are protected by restrictive covenants only to a limited extent.

The indenture governing the Notes does not contain any financial or operating covenants or restrictions on the payment of dividends, the incurrence of indebtedness or the issuance or repurchase of securities by us or any of our subsidiaries. The indenture does not contain covenants or other provisions to afford protection to holders of the Notes in the event of a fundamental change except as defined. We could engage in many types of transactions, such as acquisitions, refinancings or recapitalizations that could substantially affect our capital structure and the value of the Notes and shares of our common stock but may not constitute a fundamental change that permits holders to require us to purchase their Notes. For these reasons, noteholders should not consider the covenants in the indenture or the fundamental change purchase feature of the Notes as significant factors in evaluating whether to invest in the Notes.

The issuance of shares of common stock upon conversions of the Notes will dilute the ownership interest of our existing stockholders, including holders who had previously converted their Notes.

The issuance of shares of common stock upon the conversion of some or all of the Notes will dilute the ownership interests of our existing stockholders. Any sales in the public market of such shares of our common stock could adversely affect prevailing market prices of our common stock. In addition, the existence of the Notes may encourage short selling by market participants because the conversion of the Notes could depress the price of our common stock.

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Noteholders are not entitled to any rights with respect to our common stock, but are subject to all changes made with respect to our common stock to the extent noteholders convert their Notes and receive shares of our common stock.

Holders who convert their Notes will not be entitled to any rights with respect to our common stock (including, without limitation, voting rights and rights to receive any dividends or other distributions on our common stock) until the conversion date relating to such Notes, but holders of Notes will be subject to all changes affecting our common stock. For example, if an amendment is proposed to our second amended and restated certificate of incorporation, as amended or our amended and restated by-laws requiring stockholder approval and the record date for determining the stockholders of record entitled to vote on the amendment occurs prior to the conversion date with respect to any Notes surrendered for conversion, then the holder surrendering such Notes will not be entitled to vote on the amendment, although such holder will nevertheless be subject to any changes affecting our common stock.

Upon conversion of the Notes, holders may receive less valuable consideration than expected because the value of our common stock may decline after they exercise their conversion right but before we settle our conversion obligation.

Under the Notes, a converting holder will be exposed to fluctuations in the value of our common stock during the period from the date such holder surrenders Notes for conversion until the date we settle our conversion obligation.

Upon conversion of the Notes, we will be required to deliver the shares of our common stock, together with cash for any fractional share, on the third business day following the relevant conversion date. Accordingly, if the price of our common stock decreases during this period, the value of the shares that you receive will be adversely affected and would be less than the conversion value of the Notes on the conversion date.

The fundamental change purchase feature of the Notes may delay or prevent an otherwise beneficial attempt to take over our company.

The terms of the Notes require us to offer to purchase the Notes for cash in the event of a fundamental change, as defined. A non-stock takeover of our company may trigger the requirement that we purchase the Notes. This feature may have the effect of delaying or preventing a takeover of our company that would otherwise be beneficial to investors.

Risks Related to Our Common Stock

The market price of our common stock may be volatile and adversely affected by several factors.

The market price of our common stock could fluctuate significantly in response to various factors and events, including:

- our ability to integrate operations, technology, products and services;
- our ability to execute our business plan;
- operating results below expectations;
- announcements concerning product development results, including clinical trial results, or intellectual property rights of others;
- litigation or public concern about the safety of our potential products;
- our issuance of additional securities, including debt or equity or a combination thereof, necessary to fund our operating expenses;
- announcements of technological innovations or new products by us or our competitors;
- loss of any strategic relationship;
- industry developments, including, without limitation, changes in healthcare policies or practices or third-party reimbursement policies;
- economic and other external factors;
- period-to-period fluctuations in our financial results; and
- whether an active trading market in our common stock develops and is maintained.

In addition, the securities markets have from time to time experienced significant price and volume fluctuations that are unrelated to the operating performance of particular companies. These market fluctuations may also materially and adversely affect the market price of our common stock.

We have not paid cash dividends in the past and do not expect to pay cash dividends in the foreseeable future. Any return on investment in shares of common stock may be limited to the value of our common stock.

We have never paid cash dividends on our common stock and do not anticipate paying cash dividends on our common stock in the foreseeable future. The payment of dividends on our capital stock will depend on our earnings, financial condition and other business and economic factors affecting us at such time as the board of directors may consider relevant. If we do not pay dividends, our common stock may be less valuable because a return on any investment in shares of our common stock will only occur if the common stock price appreciates.

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A sale of a substantial number of shares of the common stock may cause the price of our common stock to decline.

If our stockholders sell, or the market perceives that our stockholders intend to sell for various reasons, substantial amounts of our common stock in the public market may make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deem reasonable or appropriate.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the common stock of biotechnology and biopharmaceutical companies. These broad market fluctuations may cause the market price of our common stock to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of our securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies have experienced significant stock price volatility in recent years. We may become involved in this type of litigation in the future. Litigation often is expensive and diverts management's attention and resources, which could adversely affect our business.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expenses related to our development programs;
- initiation or completion of clinical trials;
- any intellectual property infringement lawsuit in which we may become involved;
- regulatory developments affecting our product candidates;
- our execution of any collaborative, licensing or similar arrangements, and the timing of payments under these arrangements; and
- if plecanatide receives regulatory approval, the level of underlying demand for that product and wholesalers' buying patterns.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our common stock to fluctuate substantially.

If we fail to comply with the rules under the Sarbanes-Oxley Act of 2002 related to accounting controls and procedures, or if we discover material weaknesses and deficiencies in our internal control and accounting procedures, our stock price could decline significantly and raising capital could be more difficult.

If we fail to comply with the rules under the Sarbanes-Oxley Act of 2002 related to disclosure controls and procedures, or, if we discover material weaknesses and other deficiencies in our internal control and accounting procedures, our stock price could decline significantly and raising capital could be more difficult. Section 404 of the Sarbanes-Oxley Act requires annual management assessments of the effectiveness of our internal control over financial reporting and a report by our independent auditors addressing these assessments. If material weaknesses or significant deficiencies are discovered or if we otherwise fail to achieve and maintain the adequacy of our internal control, we may not be able to ensure that we can conclude on an ongoing basis that we have effective internal controls over financial reporting in accordance with Section 404 of the Sarbanes-Oxley Act. Moreover, effective internal controls are necessary for us to produce reliable financial reports and are important to helping prevent financial fraud. If we cannot provide reliable financial reports or prevent fraud, our business and operating results could be harmed, investors could lose confidence in our reported financial information, and the trading price of our common stock could drop significantly.

Our certificate of incorporation and bylaws and Delaware law may have anti-takeover effects that could discourage, delay or prevent a change in control, which may cause our stock price, and the value of the Notes, to decline.

Our second amended and restated certificate of incorporation, as amended and our amended and restated bylaws and Delaware law could make it more difficult for a third party to acquire us, even if closing such a transaction would be beneficial to our stockholders or holders of the Notes. We are authorized to issue up to 20,000,000 shares of preferred stock. This preferred stock may be issued in one or more series, the terms of which may be determined at the time of issuance by our board of directors without further action by stockholders. The terms of any series of preferred stock may include voting rights (including the right to vote as a series on particular matters), preferences as to dividend, liquidation, conversion and redemption rights and sinking fund provisions. No preferred stock is currently outstanding. The issuance of any preferred stock could materially adversely affect the rights of the holders of our common stock, and therefore, reduce the value of our common stock and the Notes. In particular, specific rights granted to future holders of preferred stock could be used to restrict our ability to merge with, or sell our assets to, a third party and thereby preserve control by the present management.

Provisions of our second amended and restated certificate of incorporation, as amended and our amended and restated bylaws and Delaware law also could have the effect of discouraging potential acquisition proposals or making a tender offer or delaying or preventing a change in control, including changes a stockholder or holder of the Notes might consider favorable. Such provisions may also prevent or frustrate attempts by our

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stockholders to replace or remove our management. In particular, our second amended and restated certificate of incorporation, as amended and amended and restated bylaws and Delaware law, as applicable, among other things:

- provide the board of directors with the ability to alter the bylaws without stockholder approval;
- place limitations on the removal of directors; and
- provide that vacancies on the board of directors may be filled by a majority of directors in office, although less than a quorum.

We are subject to Section 203 of the Delaware General Corporation Law which, subject to certain exceptions, prohibits business combinations between a publicly-held Delaware corporation and an interested stockholder, which is generally defined as a stockholder who becomes a beneficial owner of 15% or more of a Delaware corporation's voting stock for a three-year period following the date that such stockholder became an interested stockholder. These provisions are expected to discourage certain types of coercive takeover practices and inadequate takeover bids and to encourage persons seeking to acquire control of us to first negotiate with our board. These provisions may delay or prevent someone from acquiring or merging with us, which may cause the market price of our common stock and the value of the Notes to decline.

FORWARD-LOOKING STATEMENTS

This prospectus and any accompanying prospectus supplement, including the documents that we incorporate by reference, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act) and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). Any statements in this prospectus and any accompanying prospectus supplement about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. These statements are often, but not always, made through the use of words or phrases such as believe, will, expect, anticipate, estimate, intend, plan and would. For example, statements concerning financial condition, possible or assumed future results of operations, growth opportunities, industry ranking, plans and objectives of management, markets for our common stock and future management and organizational structure are all forward-looking statements. Forward-looking statements are not guarantees of performance. They involve known and unknown risks, uncertainties and assumptions that may cause actual results, levels of activity, performance or achievements to differ materially from any results, levels of activity, performance or achievements expressed or implied by any forward-looking statement.

Any forward-looking statements are qualified in their entirety by reference to the risk factors discussed throughout this prospectus and any accompanying prospectus supplement. Some of the risks, uncertainties and assumptions that could cause actual results to differ materially from estimates or projections contained in the forward-looking statements include but are not limited to:

- market conditions;
- our liquidity and our expectations regarding our needs for and ability to raise additional capital;
- our ability to compete with larger better financed pharmaceutical companies;

- our uncertainty of developing a marketable product;
- our expectations regarding clinical trials, the timing of clinical results, development timelines and regulatory filings and submissions for our product candidates;
- the timing, progress, costs and results of our current Phase 3 12-week clinical trials of plecanatide in CIC patients;
- the timing, progress, costs and results of our current Phase 2 clinical trial of dolcanatide for the treatment of OIC patients;
- our ability to obtain regulatory approvals;
- our ability to maintain and protect intellectual property rights;
- our ability to control product development costs;
- we may not be able to attract and retain key employees;
- we may not be able to compete effectively;
- we may not be able enter into new strategic collaborations;
- our involvement in patent and other intellectual property litigation could be expensive and could divert management's attention;
- the possibility that there will be no market acceptance for our products; and
- changes in third-party reimbursement policies could adversely affect potential future sales of any of our products that are approved for marketing.

The foregoing list sets forth some, but not all, of the factors that could affect our ability to achieve results described in any forward-looking statements. You should read this prospectus and any accompanying prospectus supplement and the documents that we reference herein and therein and have filed as exhibits to the registration statement, of which this prospectus is part, completely and with the understanding that our actual future results may be materially different from what we expect. You should assume that the information appearing in this prospectus and any accompanying prospectus supplement is accurate as of the date on the front cover of this prospectus or such prospectus supplement only. Because the risk factors referred to on page of this prospectus and incorporated herein by reference, could cause actual results or outcomes to differ materially from those expressed in any forward-looking

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statements made by us or on our behalf, you should not place undue reliance on any forward-looking statements. Further, any forward-looking statement speaks only as of the date on which it is made, and we undertake no obligation to update any forward-looking statement to reflect events or circumstances after the date on which the statement is made or to reflect the occurrence of unanticipated events. New factors emerge from time to time, and it is not possible for us to predict which factors will arise. In addition, we cannot assess the impact of each factor on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements. We qualify all of the information presented in this prospectus and any accompanying prospectus supplement, and particularly our forward-looking statements, by these cautionary statements.

USE OF PROCEEDS

Except as described in any prospectus supplement and any free writing prospectus in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered under this prospectus for general corporate purposes, including research and development, the development and commercialization of our products, general and administrative expenses, license or technology acquisitions, and working capital and capital expenditures. We may also use the net proceeds to repay any debts and/or invest in or acquire complementary businesses, products or technologies, although we have no current commitments or agreements with respect to any such investments or acquisitions as of the date of this prospectus. We have not determined the amount of net proceeds to be used specifically for the foregoing purposes. As a result, our management will have broad discretion in the allocation of the net proceeds and investors will be relying on the judgment of our management regarding the application of the proceeds of any sale of the securities. Pending use of the net proceeds, we intend to invest the proceeds in short-term, investment-grade, interest-bearing instruments.

Each time we offer securities under this prospectus, we will describe the intended use of the net proceeds from that offering in the applicable prospectus supplement. The actual amount of net proceeds we spend on a particular use will depend on many factors, including, our future capital expenditures, the amount of cash required by our operations, and our future revenue growth, if any. Therefore, we will retain broad discretion in the use of the net proceeds.

THE SECURITIES WE MAY OFFER

We may offer shares of common stock, shares of preferred stock, debt securities or warrants to purchase common stock, preferred stock or debt securities, or any combination of the foregoing, either individually or as units comprised of one or more of the other securities. We may offer up to \$250,000,000 of securities under this prospectus. If securities are offered as units, we will describe the terms of the units in a prospectus supplement.

DESCRIPTION OF CAPITAL STOCK

General

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

As of the date of this prospectus, our authorized capital stock consisted of 350,000,000 shares of common stock, \$0.0001 par value per share, and 20,000,000 shares of preferred stock. Our board of directors may establish the rights and preferences of the preferred stock from time to time. As of June 30, 2015, there were 106,971,126 shares of our common stock issued and outstanding and no shares of preferred stock issued and outstanding.

Common Stock

Holders of our common stock are entitled to one vote per share. Our Second Amended and Restated certificate of incorporation, as amended, does not provide for cumulative voting. Holders of our common stock are entitled to receive ratably such dividends, if any, as may be declared by our board of directors (the Board) out of legally available funds. However, the current policy of our Board is to retain earnings, if any, for the operation and expansion of our company. Upon liquidation, dissolution or winding-up, the holders of our common stock are entitled to share ratably in all of our assets which are legally available for distribution, after payment of or provision for all liabilities.

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The holders of our common stock have no preemptive, subscription, redemption or conversion rights.

Preferred Stock

Our second amended and restated certificate of incorporation, as amended provides that our Board may by resolution, without further vote or action by the stockholders, establish one or more classes or series of preferred stock having the number of shares and relative voting rights, designation, dividend rates, liquidation, and other rights, preferences, and limitations as may be fixed by them without further stockholder approval. Once designated by our Board, each series of preferred stock will have specific financial and other terms that will be described in a prospectus supplement. The description of the preferred stock that is set forth in any prospectus supplement is not complete without reference to the documents that govern the preferred stock. These include our second amended and restated certificate of incorporation, as amended and any certificates of designation that the Board may adopt. Prior to the issuance of shares of each series of preferred stock, the Board is required by the General Corporate Law of the State of Delaware (the "DGCL") and the second amended and restated certificate of incorporation, as amended to adopt resolutions and file a certificate of designation with the Secretary of State of the State of Delaware. The certificate of designation fixes for each class or series the designations, powers, preferences, rights, qualifications, limitations and restrictions, including, but not limited to, some or all of the following:

- the distinctive designation of such series and the number of shares which shall constitute such series, which number may be increased (except where otherwise provided by the Board in creating such series) or decreased (but not below the number of shares thereof then outstanding) from time to time by resolution of the Board;
- the rate and manner of payment of dividends payable on shares of such series, including the dividend rate, date of declaration and payment, whether dividends shall be cumulative, and the conditions upon which and the date from which such dividends shall be cumulative;
- whether shares of such series shall be redeemed, the time or times when, and the price or prices at which, shares of such series shall be redeemable, the redemption price, the terms and conditions of redemption, and the sinking fund provisions, if any, for the purchase or redemption of such shares;
- the amount payable on shares of such series and the rights of holders of such shares in the event of any voluntary or involuntary liquidation, dissolution or winding up of the affairs of the Company;
- the rights, if any, of the holders of shares of such series to convert such shares into, or exchange such shares for, shares of common stock, other securities, or shares of any other class or series of preferred stock and the terms and conditions of such conversion or exchange;

- the voting rights, if any, and whether full or limited, of the shares of such series, which may include no voting rights, one vote per share, or such higher number of votes per share as may be designated by the Board; and
- the preemptive or preferential rights, if any, of the holders of shares of such series to subscribe for, purchase, receive, or otherwise acquire any part of any new or additional issue of stock of any class, whether now or hereafter authorized, or of any bonds, debentures, notes, or other securities of the Company, whether or not convertible into shares of stock with the Company.

The issuance of preferred stock may delay, deter or prevent a change in control.

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

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

All shares of preferred stock offered hereby will, when issued, be fully paid and nonassessable, including shares of preferred stock issued upon the exercise of preferred stock warrants or subscription rights, if any.

Although our Board has no intention at the present time of doing so, it could authorize the issuance of a series of preferred stock that could, depending on the terms of such series, impede the completion of a merger, tender offer or other takeover attempt.

Anti-Takeover Effects of Certain Provisions of our Certificate of Incorporation, Bylaws and the DGCL

Certain provisions of our second amended and restated certificate of incorporation, as amended and amended and restated bylaws, which are summarized in the following paragraphs, may have the effect of discouraging potential acquisition proposals or making a tender offer or delaying or preventing a change in control, including changes a stockholder might consider favorable. Such provisions may also prevent or frustrate attempts by our stockholders

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to replace or remove our management. In particular, the second amended and restated certificate of incorporation, as amended and amended and restated bylaws and Delaware law, as applicable, among other things:

- provide the board of directors with the ability to alter the bylaws without stockholder approval;
- place limitations on the removal of directors; and
- provide that vacancies on the board of directors may be filled by a majority of directors in office, although less than a quorum.

These provisions are expected to discourage certain types of coercive takeover practices and inadequate takeover bids and to encourage persons seeking to acquire control of us to first negotiate with its board. These provisions may delay or prevent someone from acquiring or merging with us, which may cause our market price of our common stock to decline.

Blank Check Preferred. Our Board is authorized to create and issue from time to time, without stockholder approval, up to an aggregate of 20,000,000 shares of preferred stock in one or more series and to establish the number of shares of any series of preferred stock and to fix the designations, powers, preferences and rights of the shares of each series and any qualifications, limitations or restrictions of the shares of each series.

The authority to designate preferred stock may be used to issue series of preferred stock, or rights to acquire preferred stock, that could dilute the interest of, or impair the voting power of, holders of the common stock or could also be used as a method of determining, delaying or preventing a change of control.

Advance Notice Bylaws. The amended and restated bylaws contain an advance notice procedure for stockholder proposals to be brought before any meeting of stockholders, including proposed nominations of persons for election to our Board. Stockholders at any meeting will only be able to 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 our corporate secretary timely written notice, in proper form, of the stockholder's intention to bring that business before the meeting. Although the amended and restated bylaws do not give our Board of the power to approve or disapprove stockholder nominations of candidates or proposals regarding other business to be conducted at a special or annual meeting, the amended and restated bylaws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed or may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of us.

Interested Stockholder Transactions. We are subject to Section 203 of the DGCL which, subject to certain exceptions, prohibits business combinations between a publicly-held Delaware corporation and an interested stockholder, which is generally defined as a stockholder who becomes a beneficial owner of 15% or more of a Delaware corporation's voting stock for a three-year period following the date that such stockholder became an interested stockholder.

Limitations on Liability, Indemnification of Officers and Directors and Insurance

The DGCL authorizes corporations to limit or eliminate the personal liability of directors to corporations and their stockholders for monetary damages for breaches of directors' fiduciary duties as directors and our amended and restated certificate of incorporation will include such an exculpation provision. Our certificate of incorporation and by-laws will include provisions that indemnify, to the fullest extent allowable under the DGCL, the personal liability of directors or officers for monetary damages for actions taken as a director or officer of us, or for serving at our request as a director or officer or another position at another corporation or enterprise, as the case may be. Our certificate of incorporation and by-laws will also provide that we must indemnify and advance reasonable expenses to our directors and officers, subject to our receipt of an undertaking from the indemnified party as may be required under the DGCL. Our second amended and restated certificate of incorporation, as amended, expressly authorizes us to carry directors' and officers' insurance to protect us, our directors, officers and certain employees for some liabilities. The limitation of liability and indemnification provisions in our amended and restated certificate of incorporation and by-laws may discourage stockholders from bringing a lawsuit against directors for breach of their fiduciary duty. These provisions may also have the effect of reducing the likelihood of derivative litigation against our directors and officers, even though such an action, if successful, might otherwise benefit us and our stockholders. However, these provisions do not limit or eliminate our rights, or those of any stockholder, to seek non-monetary relief such as injunction or rescission in the event of a breach of a director's duty of care. The provisions will not alter the liability of directors under the federal securities laws. In addition, your investment may be adversely affected to the extent that, in a class action or direct suit, we pay the costs of settlement and damage awards against directors and officers pursuant to these indemnification provisions. There is currently no pending material litigation or proceeding against any of our directors, officers or employees for which indemnification is sought.

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Authorized but Unissued Shares

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

Transfer Agent and Registrar

The Transfer Agent and Registrar for our common stock is Philadelphia Stock Transfer, Inc.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplements or free writing prospectuses, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus. We may issue debt securities, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any future debt securities we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement or free writing prospectus. The terms of any debt securities we offer under a prospectus supplement may differ from the terms we describe below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. As of the date of this prospectus, we have no outstanding registered debt securities. Unless the context requires otherwise, whenever we refer to the indentures, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue any senior debt securities under the senior indenture that we will enter into with the trustee named in the senior indenture. We will issue any subordinated debt securities under the subordinated indenture and any supplemental indentures that we will enter into with the trustee named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

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

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all of the provisions of the indenture and any supplemental indentures applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt

securities that we may offer under this prospectus, as well as the complete indentures that contains the terms of the debt securities. Except as we may otherwise indicate, the terms of the senior indenture and the subordinated indenture are identical.

General

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

- the title;
- the principal amount being offered, and if a series, the total amount authorized and the total amount outstanding;
- any limit on the amount that may be issued;
- whether or not we will issue the series of debt securities in global form, and, if so, the terms and who the depository will be;
- the maturity date;
- whether and under what circumstances, if any, we will pay additional amounts on any debt securities held by a person who is not a United States person for tax purposes, and whether we can redeem the debt securities if we have to pay such additional amounts;

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

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

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

- the place where payments will be made;

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

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

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

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

- whether the indenture will restrict our ability or the ability of our subsidiaries to:
 - incur additional indebtedness;

 - issue additional securities;

- create liens;
- pay dividends or make distributions in respect of our capital stock or the capital stock of our subsidiaries;
- redeem capital stock;
- place restrictions on our subsidiaries' ability to pay dividends, make distributions or transfer assets;
- make investments or other restricted payments;
- sell or otherwise dispose of assets;
- enter into sale-leaseback transactions;
- engage in transactions with stockholders or affiliates;
- issue or sell stock of our subsidiaries; or
- effect a consolidation or merger;

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

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

- information describing any book-entry features;

- the applicability of the provisions in the indenture on discharge;
- whether the debt securities are to be offered at a price such that they will be deemed to be offered at an original issue discount as defined in paragraph (a) of Section 1273 of the Internal Revenue Code of 1986, as amended;
- the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof;
- the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, including any additional events of default or covenants provided with respect to the debt securities, and any terms that may be required by us or advisable under applicable laws or regulations.

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Conversion or Exchange Rights

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

Consolidation, Merger or Sale

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

Events of Default under the Indenture

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

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

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

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

- if specified events of bankruptcy, insolvency or reorganization occur.

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

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

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

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

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

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

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

- the holder has given written notice to the trustee of a continuing event of default with respect to that series;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made a written request and such holders have offered reasonable indemnity to the trustee or security satisfactory to it against any loss, liability or expense or to be incurred in compliance with instituting the proceeding as trustee; and
- the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

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

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

The indentures provide that if a default occurs and is continuing and is actually known to a responsible officer of the trustee, the trustee must mail to each holder notice of the default within the earlier of 90 days after it occurs and 30 days after it is known by a responsible officer of the trustee or written notice of it is received by the trustee, unless such default has been cured or waived. Except in the case of a default in the payment of principal or premium of, or interest on, any debt security or certain other defaults specified in an indenture, the trustee shall be protected in withholding such notice if and so long as the Board of Directors, the executive committee or a trust committee of directors, or responsible officers of the trustee, in good faith determine that withholding notice is in the best interests of holders of the relevant series of debt securities.

Modification of Indenture; Waiver

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

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

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

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

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

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

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

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

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

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

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

- extending the stated maturity of the series of debt securities;

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

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

Discharge

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

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

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

- maintain paying agencies;

- hold monies for payment in trust;

- recover excess money held by the trustee;

- compensate and indemnify the trustee; and
- appoint any successor trustee.

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

Form, Exchange and Transfer

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

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

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

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

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

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

Information Concerning the Trustee

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

Payment and Paying Agents

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

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

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

Governing Law

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

Ranking Debt Securities

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

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

Existing Senior Debt

On November 3, 2014, we closed a private offering of \$200 million aggregate principal amount of 7.50% Convertible Senior Notes due 2019 (including the full exercise of the over-allotment option granted to the initial purchasers to purchase an additional \$25 million aggregate principal amount of 7.50% Convertible Senior Notes due 2019, the Notes). The net proceeds from the offering were \$187.3 million after deducting the initial purchasers' discounts and offering expenses.

The Notes are effectively subordinated to any of our future secured debt and any liabilities of our subsidiaries. The Notes rank senior in right of payment to our future indebtedness that is expressly subordinated in right of payment to the Notes; equal in right of payment to our trade payables and other future unsecured indebtedness that is not so subordinated; effectively junior to any of our secured indebtedness to the extent of the value of the assets securing such indebtedness; and structurally junior to all future indebtedness (including trade payables) incurred by our subsidiaries. In the event of our bankruptcy, liquidation, reorganization or other winding up, our assets that secure debt ranking senior or equal in right of payment to the Notes will be available to pay

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obligations on the Notes only after the secured debt has been repaid in full. There may not be sufficient assets remaining to pay amounts due on any or all of the Notes then outstanding.

The Notes are our unsecured, senior obligations and bear interest at a rate of 7.50% per year, payable semiannually in arrears on May 1 and November 1 of each year, beginning on May 1, 2015. Accrued interest as of December 31, 2014 was \$2.5 million. The Notes will mature on November 1, 2019, unless earlier purchased or converted. The holders of the Notes have the ability to require us to repurchase the Notes in whole or in part for cash in the event of a fundamental change, as defined in the indenture agreement. In such case, the repurchase price would generally be 100% of the principal amount of the Notes plus any accrued and unpaid interest.

The Notes are convertible, at any time, into shares of our common stock at an initial conversion rate of 321.5434 shares per \$1,000 principal amount of notes, which is equivalent to an initial conversion price of \$3.11 per share. The conversion rate may be subject to adjustment upon the occurrence of certain specified events as provided in the Indenture (the "Indenture") governing the Convertible Senior Notes, dated November 3, 2014 between us and Wells Fargo Bank, National Association, as trustee. Adjustments to the conversion rate include stock dividends and distributions, splits and reverse splits, as well as the issuance of stock options, rights and warrants. Other adjustments to the conversion rate also include asset distributions and spin offs, and cash dividend and tender offers. Upon conversion of a Senior Convertible Note, we will settle the conversion obligation in unregistered shares of our common stock. We do not have the option to redeem the Notes prior to the Maturity Date.

Without the consent of Holders of 66 2/3% of the aggregate principal amount of Notes outstanding, we shall not permit any of our subsidiaries to incur or repay any debt other than debt permitted by terms of the Indenture, nor declare or pay any dividend and make any equity distributions. The Indenture also provides for customary events of default, including, but not limited to, failure to pay the principal or interest on any Note, pay the fundamental change purchase price or deliver shares of common stock.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements and free writing prospectuses, summarizes the material terms and provisions of the warrants that we may offer under this prospectus, which may consist of warrants to purchase common stock, preferred stock or debt securities and may be issued in one or more series. Warrants may be offered independently or together with common stock, preferred stock or debt securities offered by any prospectus supplement, and may be attached to or separate from those securities. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants that we may offer in more detail in the applicable prospectus supplement and any applicable free writing prospectus. The terms of any warrants offered under a prospectus supplement may differ from the terms described below. However, no prospectus supplement will fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We will issue the warrants under a warrant agreement that we will enter into with a warrant agent to be selected by us. The warrant agent will act solely as an agent of ours in connection with the warrants and will not act as an agent for the holders or beneficial owners of the warrants. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from a current report on Form 8-K that we file with the SEC, the form of warrant agreement, including a form of warrant certificate, that describes the terms of the particular series of warrants we are offering before the issuance of the related series of warrants. The following summaries of material provisions of the warrants and the warrant agreements are subject to, and qualified in their entirety by reference to, all the provisions of the warrant agreement and warrant certificate applicable to a particular series of warrants. We urge you to read the applicable prospectus supplement and any applicable free writing prospectus related to the particular series of warrants that we sell under this prospectus, as well as the complete

warrant agreements and warrant certificates that contain the terms of the warrants.

General

We will describe in the applicable prospectus supplement the terms relating to a series of warrants, including:

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- if applicable, the date on and after which the warrants and the related securities will be separately transferable;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;

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- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;

- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;

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

- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;

- the dates on which the right to exercise the warrants will commence and expire;

- the manner in which the warrant agreements and warrants may be modified;

- United States federal income tax consequences of holding or exercising the warrants;

- the terms of the securities issuable upon exercise of the warrants; and

- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture; or

- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

Holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to the warrant agent in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to the warrant agent.

Upon receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will issue and deliver the securities purchasable upon such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Enforceability of Rights by Holders of Warrants

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

DESCRIPTION OF UNITS

The following description, together with the additional information we may include in any applicable prospectus supplements and free writing prospectuses, summarizes the material terms and provisions of the units that we may offer under this prospectus.

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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. However, no prospectus supplement will fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from a current report on Form 8-K 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 sell under this prospectus, as well as the complete unit agreement and any supplemental agreements that contain the terms of the units.

General

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

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

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement that differ from those described below; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

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

Issuance in Series

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

Enforceability of Rights by Holders of Units

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

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

LEGAL OWNERSHIP OF SECURITIES

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

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Book-Entry Holders

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

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

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

Street Name Holders

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

For securities held in street name, we or any applicable trustee or depositary will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we or any such trustee or depositary will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not legal holders, of those securities.

Legal Holders

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

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

Special Considerations for Indirect Holders

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

- how it handles securities payments and notices;
- whether it imposes fees or charges;
- how it would handle a request for the holders' consent, if ever required;
- whether and how you can instruct it to send you securities registered in your own name so you can be a legal holder, if that is permitted in the future;
- how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and

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

Global Securities

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

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

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under **Special Situations When A Global Security Will Be Terminated**. As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and legal holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with another institution that does. Thus, an investor whose security is represented by a global security will not be a legal holder of the security, but only an indirect holder of a beneficial interest in the global security.

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

Special Considerations For Global Securities

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

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

- an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;
- an investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;
- an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;
- an investor may not be able to pledge his or her interest in the global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;
- the depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in the global security. We and any applicable trustee have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in the global security. We and the trustee also do not supervise the depositary in any way;
- the depositary may, and we understand that DTC will, require that those who purchase and sell interests in the global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and
- financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in the global security, may also have their own policies affecting payments, notices and other matters relating to the securities. There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries

Special Situations When A Global Security Will Be Terminated

In a few special situations described below, a global security will terminate and interests in it will be exchanged for physical

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certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own names, so that they will be direct holders. We have described the rights of holders and street name investors above.

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

- if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or
- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

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

PLAN OF DISTRIBUTION

We may sell the securities being offered hereby in one or more of the following ways from time to time:

- through agents to the public or to investors;
- to underwriters for resale to the public or to investors;
- negotiated transactions;

- block trades;
- directly to investors; or
- through a combination of any of these methods of sale.

As set forth in more detail below, the securities may be distributed from time to time in one or more transactions:

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

We will set forth in a prospectus supplement the terms of that particular offering of securities, including:

- the name or names of any agents or underwriters;
- the purchase price of the securities being offered and the proceeds we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional securities from us;
- any agency fees or underwriting discounts and other items constituting agents or underwriters compensation;

- any initial public offering price;
- any discounts or concessions allowed or re-allowed or paid to dealers; and
- any securities exchanges or markets on which such securities may be listed.

Only underwriters named in the prospectus supplement are underwriters of the securities offered by the prospectus supplement.

If underwriters are used in an offering, we will execute an underwriting agreement with such underwriters and will specify the name of each underwriter and the terms of the transaction (including any underwriting discounts and other terms constituting

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compensation of the underwriters and any dealers) in a prospectus supplement. The securities may be offered to the public either through underwriting syndicates represented by managing underwriters or directly by one or more investment banking firms or others, as designated. If an underwriting syndicate is used, the managing underwriter(s) will be specified on the cover of the prospectus supplement. If underwriters are used in the sale, the offered securities will be acquired by the underwriters for their own accounts and may be resold from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. Any public offering price and any discounts or concessions allowed or re-allowed or paid to dealers may be changed from time to time. Unless otherwise set forth in the prospectus supplement, the obligations of the underwriters to purchase the offered securities will be subject to conditions precedent and the underwriters will be obligated to purchase all of the offered securities if any are purchased.

We may grant to the underwriters options to purchase additional securities to cover over-allotments, if any, at the public offering price, with additional underwriting commissions or discounts, as may be set forth in a related prospectus supplement. The terms of any over-allotment option will be set forth in the prospectus supplement for those securities.

If we use a dealer in the sale of the securities being offered pursuant to this prospectus or any prospectus supplement, 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. The names of the dealers and the terms of the transaction will be specified in a prospectus supplement.

We may sell the securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, any agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by institutional investors to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

In connection with the sale of the securities, underwriters, dealers or agents may receive compensation from us or from purchasers of the common stock for whom they act as agents in the form of discounts, concessions or commissions. Underwriters may sell the securities to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters or commissions from the purchasers for whom they may act as agents. Underwriters, dealers and agents that participate in the distribution of the securities, and any institutional investors or others that purchase common stock directly and then resell the securities, may be deemed to be underwriters, and any discounts or commissions received by them from us and any profit on the resale of the common stock by them may be deemed to be underwriting discounts and commissions under the Securities Act.

We may provide agents and underwriters with indemnification against particular civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to such liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

In addition, we may enter into derivative transactions with third parties (including the writing of options), or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement indicates, in connection with such a transaction, the third parties may, pursuant to this prospectus and the applicable prospectus supplement, sell securities covered by this prospectus and the applicable prospectus supplement. If so, the third party may use securities borrowed from us or others to settle such sales and may use securities received from us to close out any related short positions. We may also loan or pledge securities covered by this prospectus and the applicable prospectus supplement to third parties, who may sell the loaned securities or, in an event of default in the case of a pledge, sell the pledged securities pursuant to this prospectus and the applicable prospectus supplement. The third party in such sale transactions will be an underwriter and will be identified in the applicable prospectus supplement or in a post-effective amendment.

To facilitate an offering of a series of securities, persons participating in the offering may engage in transactions that stabilize, maintain, or otherwise affect the market price of the securities. This may include over-allotments or short sales of the securities, which involves the sale by persons participating in the offering of more securities than have been sold to them by us. In those circumstances, such persons would cover such over-allotments or short positions by purchasing in the open market or by exercising the over-allotment option granted to those persons. In addition, those persons may stabilize or maintain the price of the securities by bidding for or purchasing securities in the open market or by imposing penalty bids, whereby selling concessions allowed to underwriters or dealers participating in any such offering may be reclaimed if 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. Such transactions, if commenced, may be discontinued at any time. We make no representation or prediction as to the direction or magnitude of any effect that the transactions described above, if implemented, may have on the price of our securities.

Unless otherwise specified in the applicable prospectus supplement, each class or series of securities will be a new issue with no established trading market, other than our common stock, which is listed on The NASDAQ Global Select Market. We may elect to list any

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other class or series of securities on any exchange or market, but we are not obligated to do so. It is possible that one or more underwriters may make a market in a class or series of securities, but the underwriters will not be obligated to do so and may discontinue any market making at any time without notice. We cannot give any assurance as to the liquidity of the trading market for any of the securities.

In order to comply with the securities laws of some states, if applicable, the securities offered pursuant to this prospectus will be sold in those states only through registered or licensed brokers or dealers. In addition, in some states securities may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and complied with.

Any underwriter may engage in over-allotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Securities Exchange Act of 1934, as amended, or the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of these activities at any time.

Any underwriters who are qualified market makers on the The NASDAQ Global Select Market may engage in passive market making transactions in the securities on the The NASDAQ Global Select Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the securities. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security. If all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

LEGAL MATTERS

The validity of the issuance of the securities offered hereby will be passed upon for us by Sichenzia Ross Friedman Fercence LLP, New York, New York. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The financial statements as of December 31, 2014 and 2013 and for each of the three years in the period ended December 31, 2014 and management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2014 incorporated by reference in this Prospectus have been so incorporated in reliance on the reports of BDO USA, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus constitutes a part of a registration statement on Form S-3 filed under the Securities Act. As permitted by the SEC's rules, this prospectus and any prospectus supplement, which form a part of the registration statement, do not contain all the information that is included in the registration statement. You will find additional information about us in the registration statement. Any statements made in this prospectus or any prospectus supplement concerning legal documents are not necessarily complete and you should read the documents that are filed as exhibits to the registration statement or otherwise filed with the SEC for a more complete understanding of the document or matter.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read, without charge, and copy the documents we file at the SEC's public reference rooms in Washington, D.C. at 100 F Street, NE, Room 1580, Washington, DC 20549, or in New York, New York and Chicago, Illinois. 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 further information on the public reference rooms. Our SEC filings are also available to the public at no cost from the SEC's website at <http://www.sec.gov>. In addition, we make available on or through our Internet site copies of these reports as soon as reasonably practicable after we electronically file or furnish them to the SEC. Our Internet site can be found at <http://www.synergypharma.com>.

INCORPORATION OF DOCUMENTS BY REFERENCE

We have filed a registration statement on Form S-3 with the Securities and Exchange Commission under the Securities Act. This prospectus is part of the registration statement but the registration statement includes and incorporates by reference additional

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information and exhibits. The Securities and Exchange Commission permits us to incorporate by reference the information contained in documents we file with the Securities and Exchange Commission, which means that we can disclose important information to you by referring you to those documents rather than by including them in this prospectus. Information that is incorporated by reference is considered to be part of this prospectus and you should read it with the same care that you read this prospectus. Information that we file later with the Securities and Exchange Commission will automatically update and supersede the information that is either contained, or incorporated by reference, in this prospectus, and will be considered to be a part of this prospectus from the date those documents are filed. We have filed with the Securities and Exchange Commission, and incorporate by reference in this prospectus:

- Annual Report on Form 10-K for the year ended December 31, 2014 filed on March 16, 2015;
- Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2015 filed on May 11, 2015;
- Current Reports on Form 8-K or Form 8-K/A (excluding any reports or portions thereof that are deemed to be furnished and not filed) filed on July 1, 2015, June 23, 2015, June 19, 2015, June 17, 2015, June 9, 2015, March 16, 2015, January 29, 2015, January 9, 2015 and January 8, 2015.
- our definitive proxy statement on Schedule 14A relating to our 2015 annual meeting of stockholders filed on April 14, 2015; and
- the description of our common stock contained in the Registrant's Registration Statement on Form 8-A12B/A filed with the Commission on May 2, 2012.

We also incorporate by reference all additional documents that we file with the Securities and Exchange Commission under the terms of Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act that are made after the date of the initial registration statement but prior to effectiveness of the registration statement and after the date of this prospectus but prior to the termination of the offering of the securities covered by this prospectus. We are not, however, incorporating, in each case, any documents or information that we are deemed to furnish and not file in accordance with Securities and Exchange Commission rules.

You may request, and we will provide you with, a copy of these filings, at no cost, by calling us at (212) 297-0020 or by writing to us at the following address:

Synergy Pharmaceuticals Inc.

420 Lexington Avenue, Suite 2012

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New York, New York 10170

Attn.: Gary S. Jacob, Ph.D.,

Chief Executive Officer

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The following table sets forth an estimate of the fees and expenses relating to the issuance and distribution of the securities being registered hereby, other than underwriting discounts and commissions, all of which shall be borne by the Registrant. All of such fees and expenses, except for the SEC registration fee and the FINRA filing fee, are estimated:

| | | |
|------------------------------------|----|--------|
| SEC registration fee | \$ | 29,050 |
| Transfer agent's fees and expenses | \$ | 5,000 |
| Legal fees and expenses | \$ | 30,000 |
| Printing fees and expenses | \$ | 10,000 |
| Accounting fees and expenses | \$ | 10,000 |
| Miscellaneous fees and expenses | \$ | 1,950 |
| Total | \$ | 86,000 |

*These fees are calculated based on the securities offered and the number of issuances and accordingly cannot be estimated at this time.

Item 15. Indemnification of Officers and Directors.

Section 145 (Section 145) of the Delaware General Corporation Law, as amended (the DGCL), permits indemnification of directors, officers, agents and controlling persons of a corporation under certain conditions and subject to certain limitations. Section 145 empowers a corporation to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding whether civil, criminal, administrative or investigative, by reason of the fact that he or she is or was a director, officer or agent of the corporation or another enterprise if serving at the request of the corporation. Depending on the character of the proceeding, a corporation may indemnify against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding if the person indemnified acted in good faith and in a manner he or she reasonably believed to be in or not opposed to, the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful. In the case of an action by or in the right of the corporation, no indemnification may be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine that despite the adjudication of liability such person is fairly and reasonably entitled to indemnity for such expenses which the court shall deem proper. Section 145 further provides that to the extent a present or former director or officer of a corporation has been successful in the defense of any action, suit or proceeding referred to above or in the defense of any claim, issue or matter therein, such person shall be indemnified against expenses (including attorneys' fees) actually and reasonably incurred by such person in connection therewith. The foregoing is only a summary of the described sections of the Delaware General Corporation Law and is qualified in its entirety by reference to such sections.

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Synergy's Second Amended and Restated Certificate of Incorporation, as amended and amended and restated bylaws provide that it shall indemnify each of its officers and directors to the fullest extent permitted by Section 145.

Synergy's Second Amended and Restated Certificate of Incorporation, as amended, provides that no current or former director of Synergy shall be personally liable to it or its stockholders for monetary damages for breach of fiduciary duty as a director, except to the extent such exemption from liability or limitation thereof is not permitted under the DGCL as the same exists or may hereafter be amended.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to Synergy's directors, officers and controlling persons pursuant to the foregoing provisions, or otherwise, Synergy has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

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Item 16. Exhibits.

a) Exhibits.

| Exhibit Number | Description of Document |
|-----------------------|--|
| 1.1* | Form of Underwriting Agreement |
| 3.1 | Second Amended and Restated Certificate of Incorporation of Synergy Pharmaceuticals Inc. (incorporated by reference to Exhibit 3.1 to Form 10-K filed March 15, 2012). |
| 3.2 | Amendment to the Second Amended and Restated Certificate of Incorporation of Synergy Pharmaceuticals Inc. (incorporated by reference to Exhibit 3.1 to Form 8-K filed January 17, 2013). |
| 3.3 | Amendment to the Second Amended and Restated Certificate of Incorporation of Synergy Pharmaceuticals Inc. (incorporated by reference to Exhibit 3.1 to Form 8-K filed June 16, 2015). |
| 3.4 | Amended and Restated Bylaws (incorporated by reference to Exhibit 3.2 to Form 10-K filed March 15, 2012). |
| 4.1 | Form of Senior Indenture |
| 4.2 | Form of Subordinated Indenture |
| 4.3* | Form of Senior Note |
| 4.4* | Form of Subordinated Note |
| 4.5* | Form of Warrant |
| 4.6* | Form of Warrant Agreement |
| 4.7* | Form of Unit Agreement |
| 5.1 | Opinion of Sichenzia Ross Friedman Ference LLP as to the legality of the securities being registered |
| 23.1 | Consent of Sichenzia Ross Friedman Ference LLP (included in Exhibit 5.1) |
| 23.2 | Consent of BDO USA, LLP |
| 24.1 | Power of Attorney (included on signature pages to the registration statement) |
| 25.1* | Statement of Eligibility of Trustee on Form T-1 under the Trust Indenture Act of 1939, as amended |

* To the extent applicable, to be filed by an amendment or as an exhibit to a document filed under the Securities Exchange Act of 1934, as amended, and incorporated by reference herein.

Item 17. Undertakings.

(a) The undersigned registrant hereby undertakes:

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

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

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

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

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

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(5) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

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

(6) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of the securities:

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The undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(h) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the

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registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

(j) The undersigned registrant hereby undertakes to file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act (the Act) in accordance with the rules and regulations prescribed by the SEC under section 305(b)(2) of the Act.

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Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Form S-3 to be signed on its behalf by the undersigned, thereunto duly authorized, in New York, New York, on the 2nd day of July 2015.

SYNERGY PHARMACEUTICALS INC.

By: /s/ GARY S. JACOB
Gary S. Jacob
President, Chairman of the Board and Chief Executive
Officer

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Gary S. Jacob, his true and lawful attorney-in-fact and agent with full power of substitution and re-substitution, for him/her and in his name, place and stead, in any and all capacities to sign any or all amendments (including, without limitation, post-effective amendments) to this Registration Statement, any related Registration Statement filed pursuant to Rule 462(b) under the Securities Act of 1933 and any or all pre- or post-effective amendments thereto, and to file the same, with all exhibits thereto, and all other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully for all intents and purposes as he or she might or could do in person, hereby ratifying and confirming that said attorney-in-fact and agent, or any substitute or substitutes for him, may lawfully do or cause to be done by virtue hereof. Pursuant to the requirements of the Securities Act of 1933, the following persons in the capacities and on the dates indicated have signed this Registration Statement below.

| Signature | Title | Date |
|--|---|--------------|
| /s/ GARY S. JACOB Gary S. Jacob | President, Chairman of the Board, and Chief Executive Officer (Principal Executive Officer) | July 2, 2015 |
| /s/ BERNARD F. DENOYER Bernard F. Denoyer | Senior Vice President, Finance and Secretary (Principal Financial and Accounting Officer) | July 2, 2015 |
| /s/ MELVIN K. SPIGELMAN Melvin K. Spigelman | Director | July 2, 2015 |
| /s/ ALAN JOSLYN Alan Joslyn | Director | July 2, 2015 |
| /s/ THOMAS H. ADAMS Thomas H. Adams | Director | July 2, 2015 |
| /s/ JOHN BRANCACCIO | Director | July 2, 2015 |

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John Brancaccio

/s/ CHRISTOPHER P. MCGUIGAN
Christopher P. McGuigan

Director

July 2, 2015

Timothy S. Callahan

Director

July 2, 2015

Richard J. Daly

Director

July 2, 2015