LEXICON PHARMACEUTICALS, INC./DE
Form S-3/A
December 05, 2014

AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON DECEMBER 4, 2014
Registration No. 333-200699

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
Amendment No. 1 to
FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933
Lexicon Pharmaceuticals, Inc.
(Exact name of registrant as specified in its charter)

Delaware	76-0474169
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

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8800 Technology Forest Place
The Woodlands, Texas 77381
(281) 863-3000
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

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Lonnel Coats
President and Chief Executive Officer
8800 Technology Forest Place
The Woodlands, Texas 77381
(281) 863-3000
(Name, address, including zip code, and telephone number, including area code, of agent for service)

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Copies to:

David P. Oelman
Vinson & Elkins L.L.P.
1001 Fannin, Suite 2500
Houston, Texas 77002-6760
(713) 758-3708

Brian T. Crum
Vice President and General Counsel
Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Place
The Woodlands, Texas 77381
(281) 863-3000

Approximate date of commencement of proposed sale to the public:
From time to time after this registration statement becomes effective, subject to market conditions and other factors.
If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, check the following box. o
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. x
If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.o

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

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

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act. Large accelerated filer Accelerated filer x Non-accelerated filer (Do not check if a smaller reporting company) o Smaller reporting company o

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered	Proposed Maximum Offering Price Per Share [1]	Proposed Maximum Aggregate Offering Price [1]	Amount of Registration Fee
Common Stock, par value $0.001	4,662,780 shares	$1.00	$4,662,780	542[2]

(1) Estimated solely for the purpose of calculating the amount of the registration fee based on the high and low trading price for the common stock as reported on the Nasdaq Global Select Market on December 2, 2014, in accordance with Rule 457(c) under the Securities Act.

(2) The registration fee was previously paid in connection with the filing of the original registration statement on Form S-3 on December 3, 2014.

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 which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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

SUBJECT TO COMPLETION, DATED DECEMBER 3, 2014

4,662,780 Shares

Lexicon Pharmaceuticals, Inc.

Common Stock

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This prospectus relates to the offer and sale by selling stockholders of shares of our common stock issued by us directly to the selling stockholders pursuant to an Amended and Restated Purchase Option Agreement, dated July 30, 2010, by and among us, one of our wholly-owned subsidiaries and Symphony Icon Holdings LLC. See “Selling Stockholders” beginning on page 18.

We will not receive any proceeds from the sale of the shares offered by the selling stockholders.

The selling stockholders may offer the shares from time to time through public or private transactions at prevailing market prices, at prices related to prevailing market prices or at privately negotiated prices.

Our common stock is listed on The Nasdaq Global Select Market under the symbol “LXRX”. The last reported sale price on December 3, 2014 was $0.98 per share.

Investing in our common stock involves risks. See “Risk Factors” beginning on page 5.

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

The date of this prospectus is December ___, 2014.

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You should rely only on the information contained in this prospectus and documents incorporated into this prospectus by reference. We have not authorized anyone to provide you with information different from that contained in this prospectus or the documents incorporated by reference herein. This prospectus may only be used where it is legal to sell these securities. The information contained in this prospectus, the documents incorporated by reference herein and any supplements to this prospectus are accurate only as of the dates of their respective covers or earlier dates as specified therein, regardless of the time of delivery of this prospectus or any supplement to this prospectus or of any sale of these securities.

In this prospectus, “Lexicon,” “Lexicon Pharmaceuticals,” “we,” “us” and “our” refer to Lexicon Pharmaceuticals, Inc. and its subsidiaries. We own or have rights to trademarks or trade names that we use in connection with the operation of our business. The Lexicon name and logo are registered trademarks of Lexicon Pharmaceuticals, Inc.

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LEXICON PHARMACEUTICALS, INC.

Lexicon Pharmaceuticals is a biopharmaceutical company focused on the development of breakthrough treatments for human disease. We have advanced multiple drug candidates into clinical development. We are presently devoting most of our resources to the development of our two most advanced drug candidates:

- We are developing telotristat etiprate, or LX1032, an orally-delivered small molecule drug candidate, as a treatment for carcinoid syndrome. We have completed two Phase 2 clinical trials and are presently conducting a single pivotal Phase 3 clinical trial of telotristat etiprate in carcinoid syndrome patients. The Phase 3 clinical trial of telotristat etiprate is a 12-week, placebo-controlled study of approximately 120 to 130 patients with inadequately controlled carcinoid syndrome on background somatostatin analog therapy (including at least 105 patients on octreotide therapy), followed by a 36-week, open-label extension where all patients receive telotristat etiprate. Two dose levels of telotristat etiprate, 250 mg and 500 mg, three times daily (TID), are being tested along with placebo. The primary efficacy endpoint under evaluation in the Phase 3 clinical trial is the number of daily bowel movements, with secondary efficacy endpoints including changes in urinary 5-HIAA levels, flushing episodes, abdominal pain and quality of life measures. The Phase 3 program of telotristat etiprate also includes an additional companion study in carcinoid syndrome patients who do not meet the inclusion criteria for the pivotal Phase 3 clinical trial. We presently expect to complete enrollment in the single pivotal Phase 3 clinical trial in early 2015 and report top-line data from such trial in the third quarter of 2015. If supported by such data, we anticipate filing an NDA for telotristat etiprate in carcinoid syndrome in the first quarter of 2016 with potential FDA approval and commercial launch in the second half of 2016.
- We are developing sotagliflozin, or LX4211, an orally-delivered small molecule drug candidate, as a treatment for type 1 and type 2 diabetes. We have completed two Phase 2 clinical trials of sotagliflozin in type 2 diabetes patients and an additional clinical trial of sotagliflozin in type 2 diabetes patients with renal impairment. We have also completed a Phase 2 clinical trial of sotagliflozin in type 1 diabetes patients. We are preparing for the initiation of a Phase 2 clinical trial of sotagliflozin in a younger adult type 1 diabetes population in collaboration with JDRF, from which we presently expect to report top-line data in the first quarter of 2016. We are also preparing for the initiation of Phase 3 development of sotagliflozin in type 1 diabetes in the first half of 2015. The Phase 3 development of sotagliflozin in type 1 diabetes is expected to include three Phase 3 studies, including two pivotal Phase 3 studies. Each of the pivotal Phase 3 studies are 24-week, placebo controlled studies of approximately 750 patients, which will be followed by 28-week extensions. Two dose levels of sotagliflozin, 200mg and 400mg once daily, will be tested along with placebo. The primary efficacy endpoint under evaluation will be reduction of A1C versus placebo on optimized insulin treatment at 24 weeks, with secondary endpoints including percentage of patients achieving A1C levels of less than 7%, reduction in meal-time, or bolus, insulin use and weight loss. We presently expect to report top-line data from such trials in the fourth quarter of 2016. The third Phase 3 study would be expected to enroll 1,400 patients and involve a glycemic control primary endpoint and an evaluation of safety. We also plan to conduct a dose-ranging study of sotagliflozin in patients with type 1 diabetes concurrently with our planned Phase 3 studies. We do not intend to continue development of sotagliflozin in type 2 diabetes unless we enter into a collaboration partnership.

Our most advanced drug candidates, as well as compounds from a number of additional drug discovery and development programs that we have advanced into various stages of clinical and nonclinical development, originated from our own internal drug discovery efforts. These efforts were driven by a systematic, targeted biology-driven approach in which we used gene knockout technologies and an integrated platform of advanced medical technologies to systematically study the physiological and behavioral functions of almost 5,000 genes in mice and assessed the utility of the proteins encoded by the corresponding human genes as potential drug targets. We identified and validated in living animals, or in vivo, more than 100 targets with promising profiles for drug discovery.

We are working both independently and through strategic collaborations and alliances with third parties to capitalize on our drug discovery and development programs. We seek to retain exclusive rights to the benefits of certain drug discovery and development programs by developing and commercializing drug candidates from those programs internally and to collaborate with other pharmaceutical and biotechnology companies with respect to the development and commercialization of drug candidates from other programs, particularly when the collaboration may provide us

with access to expertise and resources that we do not possess internally or are complementary to our own.

Lexicon Pharmaceuticals was incorporated in Delaware in July 1995, and commenced operations in September 1995. Our corporate headquarters are located at 8800 Technology Forest Place, The Woodlands, Texas 77381, and our telephone number is (281) 863-3000. Our common stock is listed on The Nasdaq Global Select Market under the symbol "LXRX."

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Our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 are made available free of charge on our corporate website located at www.lexpharma.com as soon as reasonably practicable after the filing of those reports with the Securities and Exchange Commission. Information found on or through our website is not incorporated herein by reference and should not be considered part of this prospectus.

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RISK FACTORS

An investment in our common stock involves risks. You should carefully consider the following risk factors, together with all of the other information included in, or incorporated by reference into, this prospectus in evaluating an investment in our common stock. If any of the following risks were to occur, our business, financial condition or results of operations could be materially adversely affected. In that case, the trading price of our common stock could decline and you could lose all or part of your investment.

Risks Related to Our Need for Additional Financing and Our Financial Results

We will need additional capital in the future and, if it is unavailable, we will be forced to significantly curtail or cease our operations. If it is not available on reasonable terms, we will be forced to obtain funds, if at all, by entering into financing agreements on unattractive terms.

As of September 30, 2014, we had $57.9 million in cash, cash equivalents and investments. In November and December 2014, we completed a concurrent public offering of our common stock, private placement of our 5.25% convertible senior notes due 2021 and private placement of common stock which resulted in net proceeds of approximately $279.2 million. We anticipate that our existing capital resources and the cash and revenues we expect to derive from collaborations and other sources will enable us to fund our currently planned operations for at least the next 12 months. However, we caution you that we may generate less cash and revenues or incur expenses more rapidly than we currently anticipate. Our currently planned operations for the next twelve months consist of (i) the completion of our single pivotal Phase 3 clinical trial of telotristat etiprate in carcinoid syndrome patients and, if successful, continued preparations for the commercialization of telotristat etiprate, (ii) a companion Phase 3 clinical trial of telotristat etiprate to study safety and 5-hydroxyindoleacetic acid in a separate patient population, with a targeted enrollment of approximately 60 patients, (iii) a Phase 2 clinical trial of sotagliflozin in a younger adult type 1 diabetes population and (iv) three concurrent Phase 3 clinical trials for sotagliflozin in type 1 diabetes, which we expect to enroll an aggregate of 2,900 patients, and a dose-ranging study of sotagliflozin. In addition, we cannot be certain as to what type and how many clinical trials the FDA, or equivalent foreign regulatory agencies, will require us to conduct in order to gain approval to market either telotristat etiprate or sotagliflozin.

Although difficult to accurately predict, the amount of our future capital requirements will be substantial and will depend on many factors, including:

- the timing and progress of our single pivotal Phase 3 clinical trial of telotristat etiprate in carcinoid syndrome patients, including completing enrollment in the trial and our ability to obtain priority review on any potential NDA submission;
- if approved, our ability to commercialize telotristat etiprate on the timeline anticipated;
- the amount and timing of payments, if any, under existing and any future collaboration agreements;
- the amount and timing of our nonclinical development expenditures;
- the timing and progress of the clinical development of telotristat etiprate and sotagliflozin, including the timing of any required regulatory actions, the outcome of our anticipated discussions with regulators and the outcome of our sotagliflozin dose-ranging study, which we are planning to conduct concurrently with our two pivotal Phase 3 efficacy trials;
- future results from clinical trials of our drug candidates;
- the cost and timing of regulatory approvals and commercialization of drug candidates that we successfully develop;
- market acceptance of products that we successfully develop and commercially launch;
- the effect of competing programs and products, and of technological and market developments;
- the filing, maintenance, prosecution, defense and enforcement of patent claims and other intellectual property rights; and
- the cost and timing of establishing or contracting for sales, marketing and distribution capabilities of any approved drug candidate.

Our capital requirements have and will continue to increase substantially as our drug candidates progress into more advanced stage clinical development. Our capital requirements will also be affected by any expenditures we make in connection with license agreements and acquisitions of and investments in complementary products and technologies.

For all of these reasons, our future capital requirements cannot easily be quantified.

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If our capital resources are insufficient to meet future capital requirements, we will need to raise additional funds to continue our currently planned operations. If we raise additional capital by issuing equity securities, our then-existing stockholders will experience dilution and the terms of any new equity securities may have preferences over our common stock. We cannot be certain that additional financing, whether debt or equity, will be available in amounts or on terms acceptable to us, if at all. We may be unable to raise sufficient additional capital on reasonable terms, and if so, we will be forced to significantly curtail or cease our operations or obtain funds, if at all, by entering into financing agreements on unattractive terms.

We have a history of net losses, and we expect to continue to incur net losses and may not achieve or maintain profitability.

We have incurred net losses since our inception, including net losses of $97.4 million for the nine months ended September 30, 2014, $104.1 million for the year ended December 31, 2013, $110.2 million for the year ended December 31, 2012 and $116.2 million for the year ended December 31, 2011. As of September 30, 2014, we had an accumulated deficit of $1.1 billion. We are unsure when we will become profitable, if ever. The size of our net losses will depend, in part, on the rate of decline or growth in our revenues and on the level of our expenses. We expect net losses to increase significantly over the next several years as we expect to make significant investments in the development and commercialization of telotristat etiprate and sotagliflozin.

We have derived substantially all of our revenues from drug discovery and development collaborations and other collaborations and technology licenses. Future revenues from our existing collaborations are uncertain because they depend, to a large degree, on the achievement of milestones and payment of royalties we earn from any future products developed under the collaborations. As a result, we depend, in part, on securing new collaboration agreements. Our ability to secure future revenue-generating agreements will depend upon our ability to address the needs of our potential future collaborators, and to negotiate agreements that we believe are in our long-term best interests. We may determine, as we have with certain of our clinical drug candidates, including telotristat etiprate (in the United States, Canada and Japan) and sotagliflozin, that our interests are better served by retaining rights to our discoveries and advancing our therapeutic programs to a later stage, which could limit our near-term revenues and increase our expenses. Given the current stage of our operations, we do not currently derive any revenues from sales of pharmaceutical products.

A large portion of our expenses is fixed, including expenses related to facilities and equipment. In addition, we expect to spend significant amounts to fund our nonclinical and clinical development activities, including the conduct of ongoing and planned clinical trials for telotristat etiprate and sotagliflozin. If successful, we will also be required to incur substantial expenditures in preparation for and to conduct commercialization activities with respect to telotristat etiprate and sotagliflozin. As a result, we will need to generate substantial additional revenues to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

Our operating results have been and likely will continue to fluctuate, and we believe that period-to-period comparisons of our operating results are not a good indication of our future performance.

Our operating results and, in particular, our ability to generate additional revenues are dependent on many factors, including:

- our ability to establish new collaborations, and the timing of such arrangements;
- the success rate of our discovery and development efforts leading to opportunities for new collaborations and licenses, as well as milestone payments and royalties;
- the timing and willingness of our collaborators to commercialize pharmaceutical products that would result in milestone payments and royalties; and
- general and industry-specific economic conditions, which may affect our and our collaborators' research and development expenditures.

Because of these and other factors, including the risks and uncertainties described in this section, our operating results have fluctuated in the past and are likely to do so in the future. Due to the likelihood of fluctuations in our revenues and expenses, we believe that period-to-period comparisons of our operating results are not a good indication of our future performance.

We have incurred substantial indebtedness that may limit cash flow available to invest in the ongoing needs of our business.

In November 2014, we sold an aggregate principal amount of $80.0 million in 5.25% convertible senior notes due 2021. We could in the future incur additional indebtedness beyond such amount, including an additional $15.0 million principal amount of such notes if the initial purchasers in that offering exercise in full their over-allotment option. We are not restricted

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under the terms of the indenture governing the notes from incurring additional debt. Our substantial debt combined with our other financial obligations and contractual commitments could have significant adverse consequences, including:

- requiring us to dedicate a substantial portion of cash flow from operations to the payment of interest on, and principal of, our debt, which will reduce the amounts available to fund working capital, capital expenditures, product development efforts and other general corporate purposes;
- increasing our vulnerability to adverse changes in general economic, industry and market conditions;
- obligating us to restrictive covenants that may reduce our ability to take certain corporate actions or obtain further debt or equity financing;
- limiting our flexibility in planning for, or reacting to, changes in our business and the industry in which we compete; and
- placing us at a competitive disadvantage compared to our competitors that have less debt or better debt servicing options.

We intend to satisfy our current and future debt service obligations with our existing cash and cash equivalents and marketable securities and funds from external sources. However, we may not have sufficient funds or may be unable to arrange for additional financing to pay the amounts due under our existing debt. Funds from external sources may not be available on acceptable terms, if at all. In addition, a failure to comply with the covenants under our existing debt instruments could result in an event of default under those instruments. In the event of an acceleration of amounts due under our debt instruments as a result of an event of default, including upon the occurrence of an event that would reasonably be expected to have a material adverse effect on our business, operations, properties, assets or condition or a failure to pay any amount due, we may not have sufficient funds or may be unable to arrange for additional financing to repay our indebtedness or to make any accelerated payments, and the lenders could seek to enforce security interests in the collateral securing such indebtedness. In addition, the covenants under our existing debt instruments and the pledge of our assets as collateral limit our ability to obtain additional debt financing.

We may not have the ability to raise the funds necessary to repurchase our 5.25% convertible senior notes due 2021 upon a fundamental change, and our future debt may contain limitations on our ability to repurchase the notes.

Holders of our 5.25% convertible senior notes due 2021 have the right to require us to repurchase their notes upon the occurrence of a fundamental change at a repurchase price equal to 100% of their principal amount, plus accrued and unpaid interest, if any. However, we may not have enough available cash or be able to obtain financing at the time we are required to make repurchases of notes surrendered therefor. In addition, our ability to repurchase the notes may be limited by law, by regulatory authority or by agreements governing our future indebtedness. Our failure to repurchase notes at a time when the repurchase is required by the indenture pursuant to which the notes were issued would constitute a default under the indenture. A default under the indenture or the fundamental change itself could also lead to a default under agreements governing our future indebtedness. 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 repurchase the notes.

Risks Related to Development of Our Drug Candidates

We have not proven our ability to successfully develop and commercialize our drug candidates.

Our success will depend upon our ability, on our own or through collaborations, to successfully develop and select an appropriate commercialization strategy for our drug candidates. We have not proven our ability to develop or commercialize drug candidates based on our drug target discoveries, and we do not know that any pharmaceutical products based on our drug target discoveries can be successfully developed or commercialized. Our strategy was historically focused principally on the discovery and development of drug candidates for targets that have not been clinically validated in humans by drugs or drug candidates generated by others. As a result, our drug candidates are subject to uncertainties as to the effects of modulating the human drug target as well as to those relating to the characteristics and activity of the particular compound.

Clinical testing of our drug candidates in humans is an inherently risky and time-consuming process that may fail to demonstrate safety and efficacy, which could result in the delay, limitation or prevention of regulatory approval.

In order to obtain regulatory approvals for the commercial sale of any products that we may develop, we will be required to complete extensive clinical trials in humans to demonstrate the safety and efficacy of our drug candidates. We or our collaborators may not be able to obtain authority from the FDA, or other equivalent foreign regulatory agencies to initiate or

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complete any clinical trials. In addition, we have limited internal resources for making regulatory filings and interacting with regulatory authorities.

Clinical trials are inherently risky and the results from nonclinical testing of a drug candidate that is under development may not be predictive of results that will be obtained in human clinical trials. In addition, the results of early human clinical trials may not be predictive of results that will be obtained in larger-scale, advanced stage clinical trials. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials, even after achieving positive results in earlier trials. Although the results of our Phase 2 proof-of-concept study of sotagliflozin in type 1 diabetes patients were positive, we cannot assure you that the planned Phase 3 clinical trials of sotagliflozin will achieve positive results. A number of factors could contribute to a lack of positive results in such Phase 3 clinical trials, including a primary endpoint in such planned Phase 3 clinical trials which has not previously been utilized for such purpose. Negative or inconclusive results from a nonclinical study or a clinical trial could cause us, one of our collaborators or the FDA to terminate a nonclinical study or clinical trial or require that we repeat or modify it. For example, concurrently with our planned Phase 3 clinical trials in our type 1 diabetes program, we plan to conduct a dose-ranging study of sotagliflozin in patients with type 1 diabetes as required by the FDA. If the results of the dose-ranging study are inconsistent with the design of our Phase 3 trials of sotagliflozin, such as suggesting that there is an effective dose of sotagliflozin in patients with type 1 diabetes lower than the doses we are studying in our Phase 3 clinical trials of sotagliflozin, we may be required to modify those Phase 3 clinical trials which could significantly delay the completion of the trials. Furthermore, we, one of our collaborators or a regulatory agency with jurisdiction over the trials may suspend clinical trials at any time if the subjects or patients participating in such trials are being exposed to unacceptable health risks or for other reasons.

Any nonclinical or clinical test may fail to produce results satisfactory to the FDA or foreign regulatory authorities. Nonclinical and clinical data can be interpreted in different ways, which could delay, limit or prevent regulatory approval. For example, the FDA suggested we study sotagliflozin in both type 1 and type 2 diabetes concurrently rather than only in type 1 diabetes. This could influence the way in which the FDA interprets the results of our trials of sotagliflozin. The FDA or institutional review boards at the medical institutions and healthcare facilities where we sponsor clinical trials may suspend any trial indefinitely if they find deficiencies in the conduct of these trials. Clinical trials must be conducted in accordance with the FDA's current Good Clinical Practices. The FDA and these institutional review boards have authority to oversee our clinical trials, and the FDA may require large numbers of subjects or patients. In addition, we must manufacture, or contract for the manufacture of, the drug candidates that we use in our clinical trials under the FDA's current Good Manufacturing Practices.

The rate of completion of clinical trials is dependent, in part, upon the rate of enrollment of patients. Patient accrual is a function of many factors, including the size of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the study, the nature of the study, the existence of competitive clinical trials and the availability of alternative treatments. Delays in planned patient enrollment may result in increased costs and prolonged clinical development, which in turn could allow our competitors to bring products to market before we do and impair our ability to commercialize our products or potential products.

We or our collaborators may not be able to successfully complete any clinical trial of a potential product within any specified time period. In some cases, we or our collaborators may not be able to complete the trial at all. Moreover, clinical trials may not show our potential products to be both safe and effective. Thus, the FDA and other regulatory authorities may not approve any products that we develop for any indication or may limit the approved indications or impose other conditions.

Risks Related to Regulatory Approval of Our Drug Candidates

Our drug candidates are subject to a lengthy and uncertain regulatory process that may not result in the necessary regulatory approvals, which could adversely affect our ability to commercialize products.

Our drug candidates, including telotristat etiprate and sotagliflozin, as well as the activities associated with their research, development and commercialization, are subject to extensive regulation by the FDA and other regulatory agencies in the United States and by comparable authorities in other countries. Failure to obtain regulatory approval for a drug candidate would prevent us from commercializing that drug candidate. We have not received regulatory approval to market any of our drug candidates in any jurisdiction and have only limited experience in preparing and

filing the applications necessary to gain regulatory approvals. The process of obtaining regulatory approvals is expensive, and often takes many years, if approval is obtained at all, and can vary substantially based upon the type, complexity and novelty of the drug candidates involved. Before a new drug application can be filed with the FDA, the drug candidate must undergo extensive clinical trials, which can take many years and may require substantial expenditures. Any clinical trial may fail to produce results satisfactory to the FDA. For example, the FDA could determine that the design of a clinical trial is inadequate to produce reliable results. Furthermore, prior to approving a new drug, the FDA typically requires that the efficacy of the drug be demonstrated in two double-blind, controlled studies. In light of the unmet medical need in carcinoid syndrome, the results of our Phase 2 clinical trials of

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telotristat etiprate and our interactions with the FDA regarding those results, we believe a single Phase 3 clinical trial of telotristat etiprate will be sufficient. However, the FDA has indicated that the trial must demonstrate statistically robust evidence of important clinical benefit and an acceptable safety profile in order to warrant consideration for marketing approval. If the FDA determines that our Phase 3 results do not have statistically robust results or clinically meaningful benefit, or if the FDA requires us to conduct additional Phase 3 clinical trials of telotristat etiprate prior to seeking marketing approval, we will incur significant additional development costs and commercialization of telotristat etiprate may be prevented or delayed. The regulatory process also requires nonclinical testing, and data obtained from nonclinical and clinical activities are susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. For example, we will need to complete certain nonclinical studies on a pre-approval basis in connection with our diabetes program, including carcinogenicity and toxicology. In our carcinoid syndrome program, we will need to conduct carcinogenicity studies on a post-approval basis and drug interaction studies on a pre-approval basis. Negative results in any of these nonclinical studies could delay or prevent approval of our product candidates. In addition, delays or rejections may be encountered based upon changes in regulatory policy for product approval during the period of product development and regulatory agency review. Changes in regulatory approval policy, regulations or statutes or the process for regulatory review during the development or approval periods of our drug candidates may cause delays in the approval or rejection of an application. For example, the FDA may expand to Phase 3 programs for type 1 diabetes its current requirement that Phase 3 programs for type 2 diabetes include studies designed to measure cardiovascular outcomes. The FDA has asked that we submit a cardiovascular risk assessment of sotagliflozin. If the risk assessment suggests a higher than acceptable cardiovascular risk or if the FDA requests that we submit cardiovascular outcome data for sotagliflozin, it could significantly delay or prevent approval. Even if the FDA or a comparable authority in another country approves a drug candidate, the approval may impose significant restrictions on the indicated uses, conditions for use, labeling, advertising, promotion, marketing and/or production of such product and may impose ongoing requirements for post-approval studies, including additional research and development and clinical trials. These agencies also may impose various civil or criminal sanctions for failure to comply with regulatory requirements, including withdrawal of product approval.

If our potential products receive regulatory approval, we or our collaborators will remain subject to extensive and rigorous ongoing regulation.

If we or our collaborators obtain initial regulatory approvals from the FDA or foreign regulatory authorities for any products that we may develop, we or our collaborators will be subject to extensive and rigorous ongoing domestic and foreign government regulation of, among other things, the research, development, testing, manufacture, labeling, promotion, advertising, distribution and marketing of our products and drug candidates. The failure to comply with these requirements or the identification of safety problems during commercial marketing could lead to the need for product marketing restrictions, product withdrawal or recall or other voluntary or regulatory action, which could delay further marketing until the product is brought into compliance. The failure to comply with these requirements may also subject us or our collaborators to stringent penalties.

Risks Related to Commercialization of Products

The commercial success of any products that we may develop will depend upon the degree of market acceptance of our products among physicians, patients, health care payors, private health insurers and the medical community.

Even if approved by the relevant regulatory authority, our ability to commercialize any products that we may develop will be highly dependent upon the extent to which these products gain market acceptance among physicians, patients, health care payors, such as Medicare and Medicaid, private health insurers, including managed care organizations and group purchasing organizations, and the medical community. If these products do not achieve an adequate level of acceptance, we may not generate adequate product revenues, if at all, and we may not become profitable. The degree of market acceptance of our drug candidates, if approved for commercial sale, will depend upon a number of factors, including:

- the effectiveness, or perceived effectiveness, of our products in comparison to competing products;
- the existence of any significant side effects, as well as their severity in comparison to any competing products;
- potential advantages over alternative treatments;
- the ability to offer our products for sale at competitive prices;

- relative convenience and ease of administration;
- the strength of marketing and distribution support; and
- sufficient third-party coverage or reimbursement.

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If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our drug candidates, we may be unable to generate product revenues.

We have no experience as a company in the sales, marketing and distribution of pharmaceutical products and do not currently have a sales and marketing organization. Developing a sales and marketing force would be expensive and time-consuming, could delay any product launch, and we may never be able to develop this capacity. To the extent that we enter into arrangements with third parties to provide sales, marketing and distribution services, our product revenues are likely to be lower than if we market and sell any products that we develop ourselves. If we are unable to establish adequate sales, marketing and distribution capabilities, independently or with others, we may not be able to generate product revenues.

If we are unable to obtain adequate coverage and reimbursement from third-party payors for any products that we may develop, our revenues and prospects for profitability will suffer.

Our ability to commercialize any products that we may develop will be highly dependent on the extent to which coverage and reimbursement for our products will be available from third-party payors, including governmental payors, such as Medicare and Medicaid, and private health insurers, including managed care organizations and group purchasing organizations. Many patients will not be capable of paying themselves for some or all of the products that we may develop and will rely on third-party payors to pay for, or subsidize, their medical needs. If third-party payors do not provide coverage or reimbursement for any products that we may develop, our revenues and prospects for profitability will suffer. In addition, even if third-party payors provide some coverage or reimbursement for our products, the availability of such coverage or reimbursement for prescription drugs under private health insurance and managed care plans often varies based on the type of contract or plan purchased.

Another factor that may negatively affect the pricing of drugs is any action regarding drug reimportation into the United States. For example, the Medicare Prescription Drug, Improvement and Modernization Act of 2003 gives discretion to the Secretary of Health and Human Services to allow drug reimportation into the United States under some circumstances from foreign countries, including countries where drugs are sold at a lower price than in the United States. Proponents of drug reimportation may attempt to pass additional legislation, which would allow direct reimportation under certain circumstances. If legislation or regulations were passed allowing the reimportation of drugs, it could decrease the price we receive for any products that we may develop, thereby negatively affecting our revenues and prospects for profitability.

In addition, in some foreign countries, particularly the countries in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, price negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement and/or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our drug candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in the commercialization of our drug candidates. Third-party payors are challenging the prices charged for medical products and services, and many third-party payors limit reimbursement for newly approved health care products. In particular, third-party payors may limit the indications for which they will reimburse patients who use any products that we may develop. Cost-control initiatives could decrease prices we might establish for products that we may develop, which would result in lower product revenues to us.

Current and future healthcare laws and regulations may negatively affect our revenues and prospects for profitability.

A primary trend in the United States and some foreign countries is toward reform and cost containment in the health care industry. The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals that may have the effect of reducing the prices that we are able to charge for products we develop. For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA, substantially modifies the framework by which healthcare is financed by both governmental and private insurers in the United States. A number of provisions contained in the PPACA have the potential to significantly affect the pharmaceutical industry, including:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs, apportioned among these entities according to their market share in certain governmental health programs;
- expansion of eligibility criteria and increases in the rebates manufacturers must pay under certain Medicaid programs;

- a new Medicare Part D coverage program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during any coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;

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- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; and
- certain reporting requirements relating to financial arrangements with, and drug samples provided to, physicians.

The PPACA and other healthcare reform measures which may be adopted in the future in the United States and foreign jurisdictions may result in more rigorous coverage criteria and significant downward pressure on the prices drug manufacturers may charge. As a result, our revenues and prospects for profitability could be significantly harmed.

Our competitors may develop products that make our products obsolete.

The biotechnology industry is highly fragmented and is characterized by rapid technological change. We face, and will continue to face, intense competition from biotechnology and pharmaceutical companies, as well as academic research institutions, clinical reference laboratories and government agencies that are pursuing research and development activities similar to ours. In addition, significant delays in the development of our drug candidates could allow our competitors to bring products to market before us, which would impair our ability to commercialize our drug candidates. Any products that we develop will compete in highly competitive markets. Further, our competitors may be more effective at using their technologies to develop commercial products. Many of the organizations competing with us have greater capital resources, larger research and development staff and facilities, more experience in obtaining regulatory approvals and more extensive product manufacturing and marketing capabilities. As a result, our competitors may be able to more easily develop products that would render our products, and those of our collaborators, obsolete and noncompetitive. For example, drug candidates are currently being developed by other pharmaceutical companies for the treatment of type 2 diabetes that act through SGLT2, one of the targets of sotagliflozin, which are in more advanced stages of development than sotagliflozin or have been approved for commercial sale by the FDA or other regulatory agencies. In addition, there may be drug candidates of which we are not aware at an earlier stage of development that may compete with our drug candidates.

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

To date, our drug candidates have been manufactured in small quantities for nonclinical and clinical trials. If any of these drug candidates are approved by the FDA or other regulatory agencies for commercial sale, we will need to manufacture them in larger quantities. We may not be able to successfully increase the manufacturing capacity, whether in collaboration with third-party manufacturers or on our own, for any of our drug 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 successfully increase the manufacturing capacity for a drug candidate, the regulatory approval or commercial launch of that drug candidate may be delayed or there may be a shortage in supply. Our drug candidates require precise, high-quality manufacturing. The failure to achieve and maintain these high manufacturing standards, 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 seriously hurt our business.

Risks Related to Our Relationships with Third Parties

We are dependent in many ways upon our collaborations with major pharmaceutical companies, including Ipsen. If we are unable to establish new collaborations, if milestones are not achieved under our collaborations or if our collaborators' efforts fail to yield pharmaceutical products on a timely basis, our opportunities to generate revenues and earn royalties will be reduced.

We have derived a substantial majority of our revenues to date from collaborative drug discovery and development alliances with a limited number of major pharmaceutical companies, including Ipsen Pharma SAS. In addition, we currently intend to seek a collaboration partner for Phase 3 development of sotagliflozin in type 2 diabetes and we cannot be certain that we will be successful in establishing such a collaborative alliance on terms acceptable to us, if at all.

Future revenues from our existing drug discovery and development alliances depend upon the achievement of milestones and payment of royalties we earn from any future products developed under the collaborations. If our relationship terminates with any of our collaborators, our reputation in the business and scientific community may suffer and revenues will be negatively impacted to the extent such losses are not offset by additional collaboration

agreements. If milestones are not achieved under our collaborations or our collaborators are unable to successfully develop products from which royalties are payable, we will not earn the revenues contemplated by those drug discovery and development collaborations. In addition, some of our alliances are exclusive and preclude us from entering into additional collaborative arrangements with other parties in the field of exclusivity.

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We have limited or no control over the resources that any collaborator may devote to the development and commercialization of products under our alliances. Any of our present or future collaborators may not perform their obligations as expected. These collaborators may breach or terminate their agreements with us or otherwise fail to conduct discovery, development or commercialization activities successfully or in a timely manner. Further, our collaborators may elect not to develop pharmaceutical products arising out of our collaborative arrangements or may not devote sufficient resources to the development, approval, manufacture, marketing or sale of these products. If any of these events occurs, we may not be able to develop or commercialize potential pharmaceutical products.

Conflicts with our collaborators could jeopardize the success of our collaborative agreements and harm our product development efforts.

We may pursue opportunities in specific disease and therapeutic modality fields that could result in conflicts with our collaborators, if any of our collaborators takes the position that our internal activities overlap with those activities that are exclusive to our collaboration. Moreover, disagreements could arise with our collaborators over rights to our intellectual property or our rights to share in any of the future revenues of compounds or therapeutic approaches developed by our collaborators. Any conflict with or among our collaborators could result in the termination of our collaborative agreements, delay collaborative research or development activities, impair our ability to renew or obtain future collaborative agreements or lead to costly and time consuming litigation. Conflicts with our collaborators could also have a negative impact on our relationship with existing collaborators, materially impairing our business and revenues. Some of our collaborators are also potential competitors or may become competitors in the future. Our collaborators could develop competing products, preclude us from entering into collaborations with their competitors or terminate their agreements with us prematurely. Any of these events could harm our product development efforts.

We rely on third parties to carry out drug development activities.

We rely on clinical research organizations and other third party contractors to carry out many of our drug development activities, including the performance of nonclinical laboratory and animal tests under the FDA's current Good Laboratory Practices regulations and the conduct of clinical trials of our drug candidates in accordance with protocols we establish. If these third parties do not successfully carry out their contractual duties or regulatory obligations or meet expected deadlines, our drug development activities may be delayed, suspended or terminated. Such a failure by these third parties could significantly impair our ability to develop and commercialize the affected drug candidates.

We lack the capability to manufacture materials for nonclinical studies, clinical trials or commercial sales and rely on third parties to manufacture our drug candidates, which may harm or delay our product development and commercialization efforts.

We currently do not have the manufacturing capabilities or experience necessary to produce materials for nonclinical studies, clinical trials or commercial sales and intend in the future to continue to rely on collaborators and third-party contractors to produce such materials. We will rely on selected manufacturers to deliver materials on a timely basis and to comply with applicable regulatory requirements, including the current Good Manufacturing Practices of the FDA, which relate to manufacturing and quality control activities. These manufacturers may not be able to produce material on a timely basis or manufacture material at the quality level or in the quantity required to meet our development timelines and applicable regulatory requirements. In addition, there are a limited number of manufacturers that operate under the FDA's current Good Manufacturing Practices and that are capable of producing such materials, and we may experience difficulty finding manufacturers with adequate capacity for our needs. If we are unable to contract for the production of sufficient quantity and quality of materials on acceptable terms, our product development and commercialization efforts may be delayed. Moreover, noncompliance with the FDA's current Good Manufacturing Practices can result in, among other things, fines, injunctions, civil and criminal penalties, product recalls or seizures, suspension of production, failure to obtain marketing approval and withdrawal, suspension or revocation of marketing approvals.

Risks Related to Our Intellectual Property

If we are unable to adequately protect our intellectual property, third parties may be able to use our products and technologies, which could adversely affect our ability to compete in the market.

Our success will depend in part upon our ability to obtain patents and maintain adequate protection of the intellectual property related to our products and technologies. The patent positions of biotechnology companies, including our

patent position, are generally uncertain and involve complex legal and factual questions. We will be able to protect our intellectual property rights from unauthorized use by third parties only to the extent that our products and technologies are covered by valid and enforceable patents or are effectively maintained as trade secrets. We will continue to apply for patents covering our products and technologies as and when we deem appropriate. Pending patent applications do not provide protection against

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competitors because they are not enforceable until they issue as patents. Further, the disclosures contained in our current and future patent applications may not be sufficient to meet statutory requirements for patentability. Once issued, patents still may not provide commercially meaningful protection. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from developing competing products and technologies. Furthermore, others may independently develop similar or alternative products or technologies or design around our patents. If anyone infringes upon our or our collaborators' patent rights, enforcing these rights may be difficult, costly and time-consuming and, as a result, it may not be cost-effective or otherwise expedient to pursue litigation to enforce those patent rights. In addition, our patents may be challenged or invalidated or may fail to provide us with any competitive advantages, if, for example, others were the first to invent or to file patent applications for these inventions.

Because patent applications can take many years to issue, there may be currently pending applications which may later result in issued patents that cover the production, manufacture, commercialization or use of our drug targets or drug candidates. If any such patents are issued to other entities, we will be unable to obtain patent protection for the same or similar discoveries that we make relating to our drug targets or drug candidates. Moreover, we may be blocked from using our drug targets or drug candidates or developing or commercializing our drug candidates, or may be required to obtain a license that may not be available on reasonable terms, if at all. Further, others may discover uses for our drug targets and drug candidates other than those covered in our issued or pending patents, and these other uses may be separately patentable. Even if we have a patent claim on a particular technology or product, the holder of a patent covering the use of that technology or product could exclude us from selling a product that is based on the same use of that product.

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States, and many companies have encountered significant problems in protecting and defending such rights in foreign jurisdictions. Many countries, including certain countries in Europe, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties (for example, if the patent owner has failed to "work" the invention in that country or the third party has patented improvements). In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of the patent. Compulsory licensing of life-saving drugs is also becoming increasingly popular in developing countries either through direct legislation or international initiatives. Such compulsory licenses could be extended to include some of our drug candidates, which could limit our potential revenue opportunities. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the aggressive enforcement of patent and other intellectual property protection, which makes it difficult to stop infringement.

We rely on trade secret protection for our confidential and proprietary information. We have taken security measures to protect our proprietary information and trade secrets, but these measures may not provide adequate protection. While we seek to protect our proprietary information by entering into confidentiality agreements with employees, collaborators and consultants, we cannot assure you that our proprietary information will not be disclosed, or that we can meaningfully protect our trade secrets. In addition, our competitors may independently develop substantially equivalent proprietary information or may otherwise gain access to our trade secrets.

We may be involved in patent litigation and other disputes regarding intellectual property rights and may require licenses from third parties for our planned nonclinical and clinical development and commercialization activities. We may not prevail in any such litigation or other dispute or be able to obtain required licenses.

Our nonclinical and clinical development efforts as well as our potential products and those of our collaborators may give rise to claims that they infringe the patents of others. We are aware that other companies and institutions are developing products acting through the same drug targets through which some of our drug candidates currently in clinical development act, have conducted research on many of the same targets that we have identified and have filed patent applications potentially covering drug targets that we have identified and certain therapeutic products addressing such targets. In some cases, patents have issued from these applications. In addition, many companies and institutions have well-established patent portfolios directed to common techniques, methods and means of developing, producing and manufacturing pharmaceutical products. These or other companies or institutions could bring legal

actions against us or our collaborators for damages or to stop us or our collaborators from engaging in certain nonclinical or clinical development activities or from manufacturing and marketing therapeutic products that allegedly infringe their patent rights. If any of these actions are successful, in addition to our potential liability for damages, these entities would likely require us or our collaborators to obtain a license in order to continue engaging in the infringing activities or to manufacture or market the infringing therapeutic products or may force us to terminate such activities or manufacturing and marketing efforts.

We may need to pursue litigation against others to enforce our patents and intellectual property rights and may be the subject of litigation brought by third parties to enforce their patent and intellectual property rights. In addition, we may become involved in litigation based on intellectual property indemnification undertakings that we have given to certain of our

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collaborators. Patent litigation is expensive and requires substantial amounts of management attention. The eventual outcome of any such litigation is uncertain and involves substantial risks.

We believe that there will continue to be significant litigation in our industry regarding patent and other intellectual property rights. We have expended and many of our competitors have expended and are continuing to expend significant amounts of time, money and management resources on intellectual property litigation. If we become involved in future intellectual property litigation, it could consume a substantial portion of our resources and could negatively affect our results of operations.

We have not sought patent protection outside of the United States for some of our inventions, and some of our licensed patents only provide coverage in the United States. As a result, our international competitors could be granted foreign patent protection with respect to our discoveries.

We have decided not to pursue patent protection with respect to some of our inventions outside the United States, both because we do not believe it is cost-effective and because of confidentiality concerns. Accordingly, our international competitors could develop, and receive foreign patent protection for, genes or gene sequences, uses of those genes or gene sequences, gene products and drug targets, assays for identifying potential therapeutic products, potential therapeutic products and methods of treatment for which we are seeking United States patent protection.

We may be subject to damages resulting from claims that we, our employees or independent contractors have wrongfully used or disclosed alleged trade secrets of their former employers.

Many of our employees and independent contractors were previously employed at universities, other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We may be subject to claims that these employees, independent contractors 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 divert management's attention. If we fail in defending such claims, in addition to paying money claims, we may lose valuable intellectual property rights or personnel. A loss of key research personnel and/or their work product could hamper or prevent our ability to commercialize certain drug candidates, which could severely harm our business.

Risks Related to Employees, Advisors and Facilities Operations

The loss of key personnel or the inability to attract and retain additional personnel could impair our ability to expand our operations.

We are highly dependent upon the principal members of our management and scientific staff, the loss of whose services might adversely impact the achievement of our objectives. Recruiting and retaining qualified medical, clinical and scientific personnel will be critical to support activities related to advancing our nonclinical and clinical development programs, and to support our collaborative arrangements. Competition is intense for experienced medical and clinical personnel, in particular, and we may be unable to retain or recruit medical and clinical personnel with the expertise or experience necessary to allow us to pursue collaborations, develop our products or expand our operations to the extent otherwise possible. Further, all of our employees are employed "at will" and, therefore, may leave our employment at any time.

Our collaborations with outside scientists may be subject to restriction and change.

We work with scientific and clinical advisors and collaborators at academic and other institutions that assist us in our nonclinical and clinical development efforts. These advisors and collaborators are not our employees and may have other commitments that limit their availability to us. Although these advisors and collaborators generally agree not to perform competing work, if a conflict of interest between their work for us and their work for another entity arises, we may lose their services. In such a circumstance, our development efforts with respect to the matters on which they were working may be significantly delayed or otherwise adversely affected. In addition, although our advisors and collaborators sign agreements not to disclose our confidential information, it is possible that valuable proprietary knowledge may become publicly known through them.

Security breaches may disrupt our operations and harm our operating results.

Our network security and data recovery measures may not be adequate to protect against computer viruses, break-ins, and similar disruptions from unauthorized tampering with our computer systems. The misappropriation, theft, sabotage or any other type of security breach with respect to any of our proprietary and confidential information that is

electronically stored, including research or clinical data, could have a material adverse impact on our business, operating results and financial

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condition. Additionally, any break-in or trespass of our facilities that results in the misappropriation, theft, sabotage or any other type of security breach with respect to our proprietary and confidential information, including research or clinical data, or that results in damage to our research and development equipment and assets could have a material adverse impact on our business, operating results and financial condition.

Risks Related to Environmental and Product Liability

We use hazardous chemicals and radioactive and biological materials in our business. Any claims relating to improper handling, storage or disposal of these materials could be time consuming and costly.

Our research and development processes have historically involved the controlled use of hazardous materials, including chemicals and radioactive and biological materials. Our operations have produced hazardous waste products. We cannot eliminate the risk of accidental contamination or discharge and any resultant injury from these materials. Federal, state and local laws and regulations govern the use, manufacture, storage, handling and disposal of hazardous materials. We may face liability for any injury or contamination that results from our use or the use by third parties of these materials, and such liability may exceed our insurance coverage and our total assets. Compliance with environmental laws and regulations may be expensive, and current or future environmental regulations may impair our research, development and production efforts.

In addition, our collaborators may use hazardous materials in connection with our collaborative efforts. In the event of a lawsuit or investigation, we could be held responsible for any injury caused to persons or property by exposure to, or release of, these hazardous materials used by these parties. Further, we may be required to indemnify our collaborators against all damages and other liabilities arising out of our development activities or products produced in connection with these collaborations.

We may be sued for product liability.

We or our collaborators may be held liable if any product that we or our collaborators develop, or any product that is made with the use or incorporation of any of our technologies, causes injury or is found otherwise unsuitable during product testing, manufacturing, marketing or sale. Although we currently have and intend to maintain product liability insurance, this insurance may become prohibitively expensive or may not fully cover our potential liabilities. Our inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of products developed by us or our collaborators. If we are sued for any injury caused by our or our collaborators' products, our liability could exceed our total assets.

Risks Related to Our Common Stock

Invus and its affiliates own a controlling interest in our outstanding common stock and may have interests which conflict with those of our other stockholders.

Invus, L.P. and Invus C.V., which we collectively refer to as Invus, and their affiliates currently own approximately 60.1% of the outstanding shares of our common stock and are thereby able to control the election and removal of our directors and determine our corporate and management policies, including potential mergers or acquisitions, asset sales, the amendment of our articles of incorporation or bylaws and other significant corporate transactions. This concentration of ownership may delay or deter possible changes in control of our company, which may reduce the value of an investment in our common stock. The interests of Invus and its affiliates may not coincide with the interests of other holders of our common stock.

Conversion of our 5.25% convertible senior notes due 2021 may dilute the ownership interest of our existing stockholders, including holders who had previously converted their notes, or may otherwise depress the price of our common stock.

The conversion of some or all of our 5.25% convertible senior notes due 2021 will dilute the ownership interests of existing stockholders to the extent we deliver shares upon conversion of any of the notes. Any sales in the public market of the common stock issuable upon such conversion 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 be used to satisfy short positions, or anticipated conversion of the notes into shares of our common stock could depress the price of our common stock.

Invus has additional rights under our stockholders' agreement with Invus, L.P. which provides Invus with substantial influence over certain significant corporate matters.

Under our stockholders' agreement with Invus, L.P., Invus has the right to designate a number of directors equal to the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates, rounded up to the nearest whole

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number of directors. Invus has designated three of the nine current members of our board of directors. While Invus has not presently exercised its director designation rights in full, it may exercise them at any time in the future in its sole discretion. To facilitate the exercise of such rights, we have agreed, upon written request from Invus, to take all necessary steps in accordance with our obligations under the stockholders' agreement to (1) increase the number of directors to the number specified by Invus (which number shall be no greater than reasonably necessary for the exercise of Invus' director designation rights under the stockholders' agreement) and (2) cause the appointment to the newly created directorships of directors so designated by Invus pursuant to its rights under the stockholders' agreement.

Invus also has the right to require proportionate representation of Invus-appointed directors on the audit, compensation and corporate governance committees of our board of directors, subject to certain restrictions. Invus-designated directors currently serve as one of the three members of each of the compensation committee and the corporate governance committee of our board of directors. No Invus-designated directors currently serve on the audit committee of our board of directors.

The provisions of the stockholders' agreement relating to Invus' rights to designate members of our board of directors and its audit, compensation and corporate governance committees will terminate if the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates falls below 10%. Invus also has the right to terminate these provisions at any time in its discretion.

Invus has preemptive rights under the stockholders' agreement to participate in future equity issuances by us, subject to certain exceptions, so as to maintain its then-current percentage ownership of our capital stock. Subject to certain limitations, Invus will be required to exercise its preemptive rights in advance with respect to certain marketed offerings, in which case it will be obligated to buy its pro rata share of the number of shares being offered in such marketed offering, including any overallotment (or such lesser amount specified in its exercise of such rights), so long as the sale of the shares were priced within a range within 10% above or below the market price on the date we notified Invus of the offering and we met certain other conditions.

The provisions of the stockholders' agreement relating to preemptive rights will terminate on the earlier to occur of August 28, 2017 and the date on which the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates falls below 10%.

Invus is entitled to certain consent rights under the stockholders' agreement, including with respect to (a) the creation or issuance of any new class or series of shares of our capital stock (or securities convertible into or exercisable for shares of our capital stock) having rights, preferences or privileges senior to or on parity with our common stock, (b) any amendment to our certificate of incorporation or bylaws, or amendment to the certificate of incorporation or bylaws of any of our subsidiaries, in a manner adversely affecting Invus' rights under the securities purchase agreement and the related agreements, (c) the repurchase, retirement, redemption or other acquisition of our or our subsidiaries' capital stock (or securities convertible into or exercisable for shares of our or our subsidiaries' capital stock), (d) any increase in the size of our board of directors to more than 12 members and (e) the adoption or proposed adoption of any stockholders' rights plan, "poison pill" or other similar plan or agreement, unless Invus is exempt from the provisions of such plan or agreement.

The provisions of the stockholders' agreement relating to those consent rights will terminate on the earlier to occur of August 28, 2017 and the date on which Invus and its affiliates hold less than 15% of the total number of outstanding shares of our common stock.

Our stock price may be extremely volatile.

The trading price of our common stock has been highly volatile, and we believe the trading price of our common stock will remain highly volatile and may fluctuate substantially due to factors such as the following:

- adverse results or delays in clinical trials;
- announcement of FDA approval or non-approval, or delays in the FDA review process, of our or our collaborators' product candidates or those of our competitors or actions taken by regulatory agencies with respect to our, our collaborators' or our competitors' clinical trials;
- the announcement of new products by us or our competitors;
- quarterly variations in our or our competitors' results of operations;

- conflicts or litigation with our collaborators;
- litigation, including intellectual property infringement and product liability lawsuits, involving us;
- failure to achieve operating results projected by securities analysts;

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- changes in earnings estimates or recommendations by securities analysts;
- financing transactions;
- developments in the biotechnology or pharmaceutical industry;
- sales of large blocks of our common stock or sales of our common stock by our executive officers, directors and significant stockholders;
- departures of key personnel or board members;
- developments concerning current or future collaborations;
- FDA or international regulatory actions;
- third-party reimbursement policies;
- acquisitions of other companies or technologies;
- disposition of any of our subsidiaries, drug programs or other technologies; and
- other factors, including factors unrelated to our operating performance or the operating performance of our competitors.

These factors, as well as general economic, political and market conditions, may materially adversely affect the market price of our common stock.

In the past, following periods of volatility in the market price of a company's securities, securities class action litigation has often been instituted. A securities class action suit against us could result in substantial costs and divert management's attention and resources, which could have a material and adverse effect on our business.

We may engage in future acquisitions, which may be expensive and time consuming and from which we may not realize anticipated benefits.

We may acquire additional businesses, technologies and products if we determine that these businesses, technologies and products complement our existing technology or otherwise serve our strategic goals. If we do undertake any transactions of this sort, the process of integrating an acquired business, technology or product may result in operating difficulties and expenditures and may not be achieved in a timely and non-disruptive manner, if at all, and may absorb significant management attention that would otherwise be available for ongoing development of our business. If we fail to integrate acquired businesses, technologies or products effectively or if key employees of an acquired business leave, the anticipated benefits of the acquisition would be jeopardized. Moreover, we may never realize the anticipated benefits of any acquisition, such as increased revenues and earnings or enhanced business synergies. Future acquisitions could result in potentially dilutive issuances of our equity securities, the incurrence of debt and contingent liabilities and amortization expenses related to intangible assets, which could materially impair our results of operations and financial condition.

Future sales of our common stock may depress our stock price.

If our stockholders sell substantial amounts of our common stock (including shares issued upon the exercise of options) in the public market, the market price of our common stock could fall. These sales also might make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deem appropriate. For example, following an acquisition, a significant number of shares of our common stock held by new stockholders may become freely tradable or holders of registration rights could cause us to register their shares for resale. Sales of these shares of common stock held by existing stockholders could cause the market price of our common stock to decline.

If we are unable to meet Nasdaq continued listing requirements, Nasdaq may take action to delist our common stock.

Our common stock trades on The Nasdaq Global Select Market, which has qualitative and quantitative listing criteria, including operating results, net assets, corporate governance, minimum trading price and minimums for public float, which is the amount of stock not held by our affiliates. If we are unable to meet Nasdaq continued listing requirements, Nasdaq may take action to delist our common stock. A delisting of our common stock could negatively impact us and our shareholders by reducing the liquidity and market price of our common stock and potentially reducing the number of investors willing to hold or acquire our common stock.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference into this prospectus contain certain information regarding our financial projections, plans and strategies that are forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and 21E of the Securities Exchange Act of 1934. We have attempted to identify forward-looking statements by terminology including “anticipate,” “believe,” “can,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “should” or “will” or the negative of these terms or other comparable terminology. These statements, which are only predictions and involve known and unknown risks, uncertainties and other important factors may include, among other things, statements which address our strategy and operating performance, events or developments that we expect or anticipate will occur in the future, such as projections of our future results of operations or of our financial condition, the status of any collaborative agreements or clinical trials, the expected timing of the completion of our ongoing and future clinical trials and the results of such trials, including top-line data, expected timing of initiation of our planned clinical trials, expected enrollment in our ongoing and future clinical trials, and our research and development efforts and anticipated trends in our business.

We have based these forward-looking statements on our current expectations and projections about future events. However, there may be events in the future that we are not able to predict accurately or which we do not fully control that could cause actual results to differ materially from those expressed or implied in our forward-looking statements. Many important factors could cause actual results to differ materially from those expressed or implied by these forward-looking statements, including those discussed under “Risk Factors” in this prospectus and any prospectus supplement and other sections of the documents incorporated by reference into this prospectus. Except as required by applicable law, we undertake no obligation to publicly release any revisions to the forward-looking statements or reflect events or circumstances after the date of this prospectus.

USE OF PROCEEDS

All of the shares offered by this prospectus are being offered and sold by the selling stockholders. We will not receive any proceeds from the sale of the shares of common stock offered by the selling stockholders.

We will pay all expenses for the registration of the selling stockholders’ offer and sale of the shares of common stock covered by this prospectus, including registration fees, the costs and expenses of our counsel and independent public accountants and the reasonable fees of one counsel for the selling stockholders. The selling stockholders will pay any underwriting discounts and commissions which they incur in selling shares of our common stock.

SELLING STOCKHOLDERS

In June 2007, we entered into a series of related agreements providing for the financing of the clinical development of certain of our drug candidates, including telotristat etiprate, along with any other pharmaceutical compositions modulating the same targets as those drug candidates. Under the financing arrangement, we exclusively licensed to Symphony Icon, Inc., at that time a wholly-owned subsidiary of Symphony Icon Holdings LLC, our intellectual property rights related to the programs and received an exclusive option to acquire all of the equity of Symphony Icon, thereby allowing us to reacquire the programs.

In July 2010, we entered into an amended and restated purchase option agreement with Holdings and Symphony Icon and simultaneously exercised our purchase option, thereby acquiring all of the equity of Symphony Icon and reacquiring the programs.

In November 2014, we received a $23 million upfront payment pursuant to our license and collaboration agreement with Ipsen for the development and commercialization of telotristat etiprate outside of the United States, Canada and Japan. Our receipt of such payment triggered our obligation to make a contingent payment of $11.5 million to Holdings pursuant to the amended terms of the purchase option. We issued the shares of common stock covered by this prospectus on December 4, 2014 in payment of 50%, or $5.75 million, of such contingent payment due to Holdings. We issued such shares directly to the selling stockholders at Holdings’ request and direction.

In connection with our entry into the amended and restated purchase option agreement and our exercise of our purchase option, we entered into an amended and restated registration rights agreement pursuant to which we agreed to register the resale of the shares of common stock issuable to Holdings and to use commercially reasonable efforts to keep the registration statement effective until the earliest of (a) the date on which the selling stockholders may sell all of the common stock covered by the registration statement without restriction under Rule 144(b)(1) under the

Securities Act of 1933, (b) the date on which the selling stockholders have sold all of the common stock covered by the registration statement or (c) two years after the final date on which common stock was issued in payment of the purchase price relating to the purchase option. All of the shares to

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be offered by the selling stockholders using this prospectus were originally issued by us in transactions exempt from the registration requirements of the Securities Act of 1933.

The selling stockholders, or their donees of 500 or fewer shares, may offer the shares of common stock covered by this prospectus from time to time. Our registration of the selling stockholders' offer and sale of such shares does not necessarily mean that the selling stockholders will sell any or all of their shares. We do not know when or in what amounts the selling stockholders may offer shares for sale. Because the selling stockholders may offer all or some of the shares pursuant to this offering, and because there are currently no agreements, arrangements or understandings with respect to the sale of any of the shares, we cannot estimate the number of the shares that will be held by the selling stockholders after completion of the offering.

If a selling stockholder transfers more than 500 shares of common stock by gift, pledge or other non-sale transfer after the effective date of the registration statement of which this prospectus is a part, the donee, pledgee or transferee may make no offer or sale under this prospectus unless and until a supplement to this prospectus has been filed or an amendment to the related registration statement has become effective.

The table below sets forth the beneficial ownership of all common stock held by each selling stockholder as of December 3, 2014 and the number of shares of common stock offered by this prospectus. Percentage of ownership is based on 719,697,188 shares of common stock outstanding on December 3, 2014.

We prepared this table based on information supplied to us by Holdings, and we have not sought to independently verify such information.

Name of Selling Stockholder	Beneficial Ownership Prior to Offering		Shares Offered Hereby	Beneficial Ownership After Offering	
	Number of Shares Beneficially Owned	Percentage ownership		Number of Shares Beneficially Owned	Percentage ownership
Symphony Capital Partners, L.P.	2,989,366	*	2,989,366	—	*
Symphony Strategic Partners, LLC	226,171	*	226,171	—	*
Howard Hughes Medical Institute	360,643	*	360,643	—	*
Stormlaunch & Co. for the benefit of Morgan Stanley Private Markets Fund III LP	288,514	*	288,514	—	*
Sailorshell & Co. for the benefit of Morgan Stanley AIP Global Diversified Fund LP	144,257	*	144,257	—	*
Mellon Bank, N.A. as Trustee for the Weyerhaeuser Company Master Retirement Trust	144,257	*	144,257	—	*
Sailorpier & Co. for the benefit of Aurora Cayman Limited	43,277	*	43,277	—	*
Nuclear Electric Insurance Ltd.	104,091	*	28,851	75,240	*
Factory Mutual Insurance Company	28,851	*	28,851	—	*
Stormbay & Co. for the benefit of Vijverpoort Huizen C.V.	28,851	*	28,851	—	*
Stormstar & Co. for the benefit of Morgan Stanley Private Markets Fund Employee	14,426	*	14,426	—	*

Investors III LP					
WHI Morula Fund	276,471	*	72,129	204,342	*
O'Connor Global Multi-Strategy Alpha Master Limited	144,257	*	144,257	—	*
RRD International, LLC	139,604	*	139,604	—	*
Douglas A. Drossman, M.D.	31,737	*	4,663	27,074	*
GFI Associates, Inc.	4,663	*	4,663	—	*

*Represents beneficial ownership of less than 1%.

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PLAN OF DISTRIBUTION

The shares covered by this prospectus may be offered and sold from time to time by the selling stockholders. The term "selling stockholders" includes pledgees, donees, transferees or other successors-in-interest who may later hold the selling stockholders' interests as a result of a gift, pledge, partnership distribution or other non-sale related transfer after the date of this prospectus. We will pay the costs and fees of registering the shares covered by this prospectus, but the selling stockholders will pay any brokerage commissions, discounts or other expenses relating to the sale of such shares, if any. We will not receive any proceeds from this offering. The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. Such sales may be made on one or more exchanges or in the over-the-counter market or otherwise, at prices and under terms then prevailing or at prices related to the then current market price or in negotiated transactions. The selling stockholders may offer and sell the shares of common stock offered by this prospectus in one or more of, or a combination of, the following methods:

- purchases by a broker-dealer or other person, as principal, and resale by a broker-dealer or other person for its own account pursuant to this prospectus;
- ordinary brokerage transactions and transactions in which the broker solicits purchasers;
- block trades in which a broker-dealer or other person so engaged will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- an over-the-counter distribution in accordance with the rules of the Nasdaq Global Select Market;
- through the Nasdaq Global Select Market or any other securities exchange or association that quotes the common stock;
- in privately negotiated transactions;
- in put or call option transactions relating to the shares; or
- otherwise through any other method permitted by applicable law or a combination of any of the above methods of sale.

In addition, the selling stockholders have advised us that they may sell shares of common stock in compliance with Rule 144, if available, or pursuant to other available exemptions from the registration requirements under the Securities Act of 1933, rather than pursuant to this prospectus.

To the extent required, this prospectus may be amended or supplemented from time to time to describe a specific plan of distribution. In connection with distributions of the shares or otherwise, the selling stockholders have advised us that they may enter into hedging transactions with broker-dealers or other financial institutions. In connection with such transactions, broker-dealers or other financial institutions may engage in short sales of the common stock in the course of hedging the positions they assume with the selling stockholders. The selling stockholders have advised us that they may also sell the common stock short and redeliver the shares to close out such short positions. The selling stockholders have advised us that they may also enter into option or other transactions with broker-dealers or other financial institutions which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction). The selling stockholders have advised us that they may also pledge shares to a broker-dealer or other financial institution, and, upon a default, such broker-dealer or other financial institution may effect sales of the pledged shares pursuant to this prospectus (as supplemented or amended to reflect such transaction).

In effecting sales, broker-dealers, agents or other persons engaged by a selling stockholder may arrange for other broker-dealers or other persons to participate. Broker-dealers or agents may receive commissions, discounts or concessions for their services from the selling stockholders in amounts to be negotiated immediately prior to the sale. Broker-dealers or other persons may also receive compensation from the purchasers of the shares covered by this prospectus for whom they act as agents or to whom they sell as principal, or both.

In offering the shares covered by this prospectus, the selling stockholders and any broker-dealers or other persons who execute sales for any such selling stockholder may be deemed to be "underwriters" within the meaning of Section 2(a)(11) of the Securities Act of 1933 in connection with such sales. In addition, the broker-dealers' or their affiliates' commissions, discounts or concessions or their profit on the resale of shares purchased by them may qualify as

underwriters' compensation under the Securities Act of 1933. If the selling stockholders qualify as "underwriters" they will be subject to the prospectus delivery requirements of the Securities Act of 1933.

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In order to comply with the securities laws of certain states, if applicable, the shares must be sold in such jurisdictions only through registered or licensed brokers or dealers. In addition, in certain states the shares 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 is complied with.

The selling stockholders have advised us that they may sell its shares at market prices prevailing at the time of sale, at prices related to such prevailing market prices, at negotiated prices or at fixed prices and that the transactions listed above may include cross or block transactions.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Securities Exchange Act of 1934 may apply to their sales of common stock and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act of 1933. The selling stockholders have advised us that they may indemnify any broker-dealer or agent that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act of 1933.

At the time a particular offer of shares is made, if required, a prospectus supplement will be distributed that will set forth the number of shares being offered and the terms of the offering, including the name of any underwriter, dealer or agent, the purchase price paid by any underwriter, any discount, commission and other item constituting compensation, any discount, commission or concession allowed or reallowed or paid to any dealer, and the proposed selling price to the public. In addition, upon being notified by a selling stockholder that a donee, pledgee, transferee or other successor-in-interest intends to sell more than 500 shares, we will file a supplement to this prospectus.

We have agreed to indemnify the selling stockholders against liabilities arising in connection with this offering, including liabilities under the Securities Act of 1933, or to contribute the payments that the selling stockholders may be required to make in that respect.

All shares offered by this prospectus by the selling stockholders will be sold subject to the terms and conditions of the amended and restated registration rights agreement described in the section entitled “Selling Stockholders.”

LEGAL MATTERS

The validity of the issuance of the common stock offered by this prospectus has been passed upon for us by Vinson & Elkins L.L.P., Houston, Texas.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2013, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP’s report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file reports, proxy statements and other information with the SEC. You may read and copy the reports, proxy statements and other information that we file with the SEC at 100 F Street, NE, Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for information and for its prescribed rates to obtain copies of such material. The SEC also maintains a website that contains reports, proxy and information statements and other information regarding registrants, like us, that file electronically with the SEC. The address of the SEC’s Internet site is http://www.sec.gov. Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and other filings with the SEC are available, free of charge, through our website, as soon as reasonably practicable after those reports or filings are electronically filed with or furnished to the SEC. Information on our website or any other website is not incorporated by reference into this prospectus or any prospectus supplement and does not constitute a part of this prospectus or any prospectus supplement.

This prospectus is part of a registration statement we filed with the SEC relating to the securities the selling stockholders may offer. As permitted by SEC rules, this prospectus does not contain all of the information we have included in the registration statement and the accompanying exhibits and schedules we filed with the SEC. You may refer to the registration

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statement, exhibits and schedules for more information about us and the securities. The registration statements, exhibits and schedules are available at the SEC or through its website.

DOCUMENTS INCORPORATED BY REFERENCE

The SEC allows us to "incorporate by reference" the information we have filed with it, which means that we can disclose important information to you by referring you to those documents. The information we incorporate by reference is an important part of this prospectus, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below that we have previously filed with the SEC and any future documents filed with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act subsequent to the date of this prospectus and prior to the termination of the offering of the securities covered by this prospectus:

- our annual report on Form 10-K for the year ended December 31, 2013;
- our quarterly reports on Form 10-Q for the quarterly periods ended March 31, June 30 and September 30, 2014;
- our current reports on Form 8-K filed on January 13, April 24, July 8, October 24, November 14, November 20, November 21 and November 28, 2014; and
- the description of our common stock contained in our registration statement on Form 8 A filed with the SEC on March 27, 2000 pursuant to Section 12 of the Securities Exchange Act of 1934, including any amendments and reports filed for the purpose of updating such description.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or in any other subsequently filed document which also is or is deemed to be incorporated by reference in this prospectus modifies or supersedes that statement. Any statement that is modified or superseded will not constitute a part of this prospectus, except as so modified or superseded. You may rely on any statement contained in this prospectus or in documents incorporated or deemed to be incorporated in this prospectus, unless that statement has been subsequently modified or superseded as described above prior to the time you make your investment decision.

Upon your written or oral request, we will provide you at no cost a copy of any or all of the documents incorporated by reference in this prospectus, other than the exhibits to those documents, unless the exhibits are specifically incorporated by reference into this prospectus. You may request a copy of these documents by contacting:

Investor Relations
Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Place
The Woodlands, Texas 77381-1160
Telephone: (281) 863-3000

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PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

The estimated expenses payable by the Registrant in connection with the issuance and distribution of the securities being registered (other than underwriting discounts and commissions) are as follows:

SEC Registration Fee	$542
Accounting Fees and Expenses	5,000
Legal Fees and Expenses	10,000
Transfer Agent and Registrar Fees	—
Miscellaneous Expenses	4,458
Total	$20,000

The reasonable fees of one counsel for the selling stockholders is included under “Legal Fees and Expenses” in the foregoing table. The selling stockholders will pay any underwriting discounts and commissions, which discounts and commissions are not included in the foregoing table.

Item 15. Indemnification of Directors and Officers.

Section 145 of the Delaware General Corporation Law (“DGCL”) provides that a corporation may 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 (other than an action by or in the right of the corporation) by reason of the fact that he is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys’ fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by him in connection with such action, suit or proceeding if he acted in good faith and in a manner he 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 conduct was unlawful. Section 145 further provides that a corporation similarly may indemnify any such person serving in any such capacity who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor by reason of the fact that he is or was a director, officer, employee or agent of the corporation or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys’ fees) actually and reasonably incurred in connection with the defense or settlement of such action or suit if he acted in good faith and in a manner he reasonably believed to be in or not opposed to the best interests of the corporation and except that no indemnification shall be made in respect of 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 Delaware Court of Chancery or such other court in which such action or suit was brought shall determine upon application that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Delaware Court of Chancery or such other court shall deem proper.

The Company’s amended and restated certificate of incorporation and second amended and restated bylaws provide that indemnification shall be to the fullest extent permitted by the DGCL for all current or former directors or officers. As permitted by the DGCL, the amended and restated certificate of incorporation provides that the Company’s directors shall have no personal liability to the Company or its stockholders for monetary damages for breach of fiduciary duty as a director, except (1) for any breach of the director’s duty of loyalty to the Company or its stockholders, (2) for acts or omissions not in good faith or which involve intentional misconduct or knowing violation of law, (3) under Section 174 of the DGCL or (4) for any transaction from which a director derived an improper personal benefit.

The Company has entered into indemnification agreements with each of its officers and directors. These agreements, among other things, require the Company to indemnify each officer and director for all expenses, including attorneys' fees, liabilities, judgments, fines, penalties, excise taxes and settlement amounts incurred by any such person in any claim, action, suit or proceeding, including any action by or in the right of the Company, arising out of the person's services as a director, officer, employee, agent or fiduciary to the Company, any subsidiary of the Company or to any other company or enterprise for which the person provides services at the Company's request.

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At present, there is no pending litigation or proceeding involving a director or officer of the Company as to which indemnification is being sought nor is the Company aware of any threatened litigation that may result in claims for indemnification by any officer or director.

Item 16. Exhibits.

Exhibit No.		Description
4.1	—	Amended and Restated Certificate of Incorporation (filed as Exhibit 3.1 to the Company's Current Report on Form 8-K dated April 26, 2012 and incorporated by reference herein).
4.2	—	Second Amended and Restated Bylaws (filed as Exhibit 3.2 to the Company's Current Report on Form 8-K dated April 26, 2012 and incorporated by reference herein).
4.3	—	Securities Purchase Agreement, dated June 17, 2007, with Invus, L.P. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated June 17, 2007 and incorporated by reference herein).
4.4	—	Amendment, dated October 7, 2009, to Securities Purchase Agreement, dated June 17, 2007, with Invus, L.P. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated October 7, 2009 and incorporated by reference herein).
4.5	—	Registration Rights Agreement, dated June 17, 2007, with Invus, L.P. (filed as Exhibit 10.3 to the Company's Current Report on Form 8-K dated June 17, 2007 and incorporated by reference herein).
4.6	—	Stockholders' Agreement, dated June 17, 2007, with Invus, L.P. (filed as Exhibit 10.4 to the Company's Current Report on Form 8-K dated June 17, 2007 and incorporated by reference herein).
4.7	—	Supplement to Transaction Agreements, dated March 15, 2010, with Invus, L.P. and Invus C.V. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated March 15, 2010 and incorporated by reference herein).
4.8	—	Supplement No. 2 to Transaction Agreements, dated February 23, 2012, with Invus, L.P. and Invus C.V. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated February 23, 2012 and incorporated by reference herein).
4.9	—	Amended and Restated Purchase Option Agreement, dated July 30, 2010, with Symphony Icon Holdings LLC and Symphony Icon, Inc. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated July 30, 2010 and incorporated by reference herein).
4.10	—	Amended and Restated Registration Rights Agreement, dated July 30, 2010, with Symphony Icon Holdings LLC (filed as Exhibit 10.2 to the Company's Current Report on Form 8-K dated July 30, 2010 and incorporated by reference herein).
4.11	—	Indenture related to the 5.25% Convertible Senior Notes due 2021, dated as of November 26, 2014, with Wells Fargo Bank, N.A. (filed as Exhibit 4.1 to the Company's Current Report on Form 8-K dated November 26, 2014 and incorporated by reference herein).
4.12	—	Form of 5.25% Convertible Senior Notes due 2021 (filed as Exhibit A to Exhibit 4.1 to the Company's Current Report on Form 8-K dated November 26, 2014 and incorporated by reference herein).
*5.1	—	Opinion of Vinson & Elkins L.L.P.
*23.1	—	Consent of Ernst & Young LLP
*23.2	—	Consent of Vinson & Elkins L.L.P. (contained in Exhibit 5.1).
*24.1	—	Power of Attorney (contained in the signature page to the Company's Registration Statement on Form S-3 (Registration No. 333-200699) and incorporated by reference herein).

* Filed herewith.

Item 17. Undertakings.

The undersigned Registrant hereby undertakes:
(a)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, as amended (the “Securities Act”);

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(ii)to reflect in the prospectus any facts or events arising after the effective date of this 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 this registration statement; and

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

provided, however, that paragraphs (a)(i) and (a)(ii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in periodic reports filed by the Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), that are incorporated by reference in this registration statement.

(b)That, for the purpose of determining any liability under the Securities Act, 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.

(c)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.

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

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the provisions described in Item 15, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Act and will be governed by the final adjudication of such issue.

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SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of The Woodlands, in the State of Texas, on December 4, 2014.

Lexicon Pharmaceuticals, Inc.

By: *

Lonnel Coats

President and Chief Executive Officer

PURSUANT TO THE REQUIREMENTS OF THE SECURITIES ACT OF 1933, AS AMENDED, THIS REGISTRATION STATEMENT HAS BEEN SIGNED BELOW BY THE FOLLOWING PERSONS IN THE CAPACITIES AND ON THE DATES INDICATED BELOW.

Signature	Title	Date
* Lonnel Coats	President, Chief Executive Officer and Director (Principal Executive Officer)	December 4, 2014
* Jeffrey L. Wade, J.D.	Executive Vice President, Corporate Development and Chief Financial Officer (Principal Financial Officer)	December 4, 2014
* James F. Tessmer	Vice President, Finance and Accounting (Principal Accounting Officer)	December 4, 2014
* Raymond Debbane	Chairman of the Board of Directors	December 4, 2014
* Philippe J. Amouyal	Director	December 4, 2014
* Samuel L. Barker, Ph.D.	Director	December 4, 2014
* Robert J. Lefkowitz, M.D.	Director	December 4, 2014
* Alan S. Nies, M.D.	Director	December 4, 2014
* Frank P. Palantoni	Director	December 4, 2014
* Christopher J. Sobecki	Director	December 4, 2014
* Judith L. Swain, M.D.	Director	December 4, 2014

*By: /s/ Jeffrey L. Wade

Jeffrey L. Wade
Pursuant to powers-of-attorney filed with the
Registration Statement on Form S-3
(333-200699) on December 3, 2014

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EXHIBIT INDEX

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