LEXICON PHARMACEUTICALS, INC.
Form 10-K
March 12, 2015

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K
(Mark One)

R ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Fiscal Year Ended December 31, 2014

or

£ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Transition Period from _____ to _____

Commission File Number: 000-30111
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)
8800 Technology Forest Place The Woodlands, Texas 77381 (Address of Principal Executive Offices and Zip Code)	(281) 863-3000 (Registrant's Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on which Registered
Common Stock, par value $0.001 per share	Nasdaq Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act of 1933. Yes o No R

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934. Yes o No R

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days. Yes R No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes R No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. R

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 definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Securities Exchange Act of 1934. (check one): Large accelerated filer o Accelerated filer R Non-accelerated filer o Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes o No R

The aggregate market value of voting stock held by non-affiliates of the registrant as of the last day of the registrant’s most recently completed second quarter was approximately $368.0 million, based on the closing price of the common stock on the Nasdaq Global Select Market on June 30, 2014 of $1.61 per share. For purposes of the preceding sentence only, our directors, executive officers and controlling stockholders are assumed to be affiliates. As of March 9, 2015, 725,145,313 shares of common stock were outstanding.

Documents Incorporated by Reference

Certain sections of the registrant’s definitive proxy statement relating to the registrant’s 2015 annual meeting of stockholders, which proxy statement will be filed under the Securities Exchange Act of 1934 within 120 days of the end of the registrant’s fiscal year ended December 31, 2014, are incorporated by reference into Part III of this annual report on Form 10-K.

Lexicon Pharmaceuticals, Inc.
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The Lexicon name and logo are registered trademarks and Genome5000™ is a trademark of Lexicon Pharmaceuticals, Inc.

In this annual report on Form 10-K, “Lexicon Pharmaceuticals,” “Lexicon,” “we,” “us” and “our” refer to Lexicon Pharmaceuticals, Inc. and its subsidiaries.

This annual report on Form 10-K contains forward-looking statements. These statements relate to future events or our future financial performance. We have attempted to identify forward-looking statements by terminology including “anticipate,” “believe,” “can,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “shou negative of these terms or other comparable terminology. These statements are only predictions and involve known and unknown risks, uncertainties and other factors, including the risks outlined under “Item 1A. Risk Factors,” that may cause our or our industry’s actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements.

Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. We are not under any duty to update any of the forward-looking statements after the date of this annual report on Form 10-K to conform these statements to actual results, unless required by law.

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PART I

Item 1. Business

Overview

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.
- 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 initiating a Phase 2 clinical trial of sotagliflozin in a younger adult type 1 diabetes population in collaboration with JDRF. We are also initiating Phase 3 development of sotagliflozin in type 1 diabetes. 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 preclinical development, originated from our own internal drug discovery efforts. These efforts were driven by a systematic, target 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 target discoveries and 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 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 our website should not be considered part of this annual report on Form 10-K.

Our Drug Development Programs

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, telotristat etiprate for carcinoid syndrome and sotagliflozin for type 1 and type 2 diabetes. We have also advanced a number of additional compounds into various stages of clinical and preclinical development.

Telotristat etiprate (LX1032)

Telotristat etiprate, or LX1032, is an orally-delivered small molecule compound that we are developing for the treatment of carcinoid syndrome. Telotristat etiprate was internally generated by our medicinal chemists and inhibits tryptophan hydroxylase, or TPH, the rate-limiting enzyme for serotonin production found primarily in enterochromaffin, or EC, cells of the gastrointestinal tract. Our scientists found that mice lacking the non-neuronal form of this enzyme, TPH1, have virtually no serotonin in the gastrointestinal tract, but maintain normal levels of serotonin in the brain. Telotristat etiprate was specifically designed to achieve enhanced systemic exposure to address disorders such as carcinoid syndrome that require regulation of serotonin levels beyond the EC cells in the gastrointestinal tract without impacting brain serotonin production.

We completed enrollment in March 2015 of a single pivotal Phase 3 clinical trial of telotristat etiprate evaluating the safety and tolerability of telotristat etiprate and its effect on symptoms associated with carcinoid syndrome. The trial enrolled 135 patients with inadequately controlled carcinoid syndrome on background somatostatin analog therapy in a randomized, double-blind, placebo-controlled study of 250mg three times daily and 500mg three times daily doses of telotristat etiprate over a 12-week treatment period, followed by a 36-week, open-label extension where all patients receive 500mg three times daily doses of telotristat etiprate. The primary efficacy endpoint under evaluation in the trial is the number of daily bowel movements, with secondary efficacy endpoints including changes in urinary 5-HIAA, the primary metabolite of serotonin and a biomarker for serotonin synthesis, 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 certain of the inclusion criteria for the pivotal Phase 3 clinical trial.

We reported top-line data in October 2012 from an open-label Phase 2 clinical trial evaluating the safety and tolerability of telotristat etiprate and its effects on symptoms associated with carcinoid syndrome. The trial enrolled 15 patients with metastatic carcinoid syndrome who were refractory to or could not tolerate somatostatin analog therapy in an open-label study of ascending doses of 150mg, 250mg, 350mg and 500mg of telotristat etiprate, administered three times daily, for 14 days on each dose until reaching the maximal dose, which was then continued until the completion of 12 weeks of therapy. The primary efficacy endpoint under evaluation in the trial was the reduction of bowel movements from baseline to week 12, with secondary endpoints including relief of symptoms and reduction in serotonin synthesis. Top-line data from the study showed that patients experienced a 46.4% median reduction from baseline at week 12, with the number of daily bowel movements steadily decreasing over time. All observed changes from baseline were statistically significant at $p<0.001$. This change corresponded with an increased proportion of patients reporting adequate relief of their carcinoid symptoms, a global assessment which also improved over time, with 75% of the patients with data at week 12 reporting improvement. Clinically relevant decreases from baseline were likewise seen for a number of key secondary endpoints, including statistically significant improvements in stool consistency ($p<0.001$) and trends of reductions which did not achieve statistical significance in abdominal pain and the number of cutaneous flushing episodes. The median percentage reductions from baseline of urinary 5 HIAA at weeks 8 and 12 were 68.3% and 72.7%, respectively (each, $p<0.05$). Telotristat etiprate was well tolerated in the study, with no dose-limiting toxicity observed. Three patients reported serious adverse events, none of which were related to telotristat etiprate, and no patient discontinued from the study due to an adverse event.

We reported top-line data in August 2011 from a Phase 2 clinical trial evaluating the safety and tolerability of telotristat etiprate and its effects on symptoms associated with carcinoid syndrome. The trial enrolled 23 patients with symptomatic carcinoid syndrome who were refractory to octreotride therapy in a double-blind, randomized, placebo-controlled study of 150mg, 250mg, 350mg and 500mg doses of telotristat etiprate, each administered three

times daily over a 28-day treatment period in combination with octreotide therapy. The efficacy endpoints under evaluation in the trial included the number of daily bowel movements, stool form, urgency, a global assessment of symptoms associated with carcinoid syndrome, flushing episodes and an assessment of pain and discomfort. Top-line data from the trial showed evidence of efficacy across multiple endpoints, including improvements in bowel movement frequency, decreased levels of urinary 5 HIAA and improvements in the assessment of pain and discomfort. Telotristat etiprate demonstrated a favorable safety profile in the trial, with no dose-limiting toxicity observed. Adverse events were generally mild to moderate and similarly distributed across all groups, including the placebo group.

Telotristat etiprate has received Fast Track status and Orphan Drug designation from the United States Food and Drug Administration, or FDA, for the treatment of gastrointestinal symptoms associated with carcinoid syndrome in patients who no longer respond to standard care. Telotristat etiprate has also received Orphan Drug designation from the Committee for Orphan Medical Products of the European Medicines Agency for the treatment of carcinoid tumors.

We have entered into a license and collaboration agreement with Ipsen Pharma SAS under which we granted Ipsen an exclusive, royalty-bearing right and license to commercialize telotristat etiprate outside of the United States, Canada and Japan.

Sotagliflozin (LX4211)

Sotagliflozin, or LX4211, is an orally-delivered small molecule compound that we are developing for the treatment of type 1 and type 2 diabetes mellitus. Sotagliflozin was internally generated by our medicinal chemists and inhibits both sodium-glucose cotransporter type 2, or SGLT2, a transporter responsible for most of the glucose reabsorption performed by the kidney, and sodium-glucose cotransporter type 1, or SGLT1, a transporter responsible for glucose and galactose absorption in the gastrointestinal tract, and to a lesser extent than SGLT2, glucose reabsorption in the kidney. Our scientists identified mice lacking SGLT1, SGLT2 or both as having potent anti-diabetic phenotypes across multiple measures of glucose control and metabolism, and found that compounds inhibiting both targets had a favorable preclinical profile relative to compounds selective for SGLT2.

Type 1 Diabetes. We reported top-line data in April 2014 from a Phase 2 clinical trial evaluating the safety and tolerability of sotagliflozin and its effects on glycemic parameters associated with type 1 diabetes. The Phase 2 trial enrolled 36 patients with type 1 diabetes. An initial cohort consisted of three patients treated with a 400 mg once daily dose of sotagliflozin for a period of four weeks. A subsequent cohort of 33 patients were enrolled in the randomized, double-blind, placebo-controlled portion of the study and were treated with a 400mg once daily dose of sotagliflozin or placebo for a period of four weeks. The primary efficacy endpoint under evaluation in the trial was reduction in bolus insulin use. Secondary endpoints included multiple parameters of glycemic control, basal and total insulin use and other metabolic, pharmacodynamic and pharmacokinetic parameters. Top-line data from the study showed that treatment with sotagliflozin demonstrated statistically significant benefits in the primary and multiple secondary endpoints. Patients treated with sotagliflozin experienced a reduction in their total daily mealtime bolus insulin dose of 32% compared to 6% for patients who received placebo (p=0.007). We also observed a significant improvement in glycemic control, with a mean hemoglobin A1c, or A1C, reduction of 0.55% in the sotagliflozin-treated group compared to a reduction of 0.06% in the placebo-treated group (p=0.002). These observations were also accompanied by significant improvement in the time spent in a glucose range of 70-180 mg/dl, a significant reduction in time in hyperglycemic range (>180 mg/dl) and no increase in hypoglycemia. Multiple measures also indicated that patients treated with sotagliflozin experienced reduced variability in blood glucose levels. Sotagliflozin was well tolerated with no discontinuations of study medication due to adverse events.

We are initiating a Phase 2 clinical trial of sotagliflozin in a younger adult type 1 diabetes population in collaboration with JDRF. We are also initiating Phase 3 development of sotagliflozin in type 1 diabetes, which 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. The third Phase 3 study is expected to enroll approximately 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.

Type 2 Diabetes. We reported top-line data in June 2012 from a Phase 2b clinical trial evaluating the safety and tolerability of sotagliflozin and its effects on glycemic parameters associated with type 2 diabetes. The Phase 2b trial enrolled 299 patients with type 2 diabetes who were not adequately controlled on metformin monotherapy in a double-blind, randomized, placebo-controlled study of 75mg once daily, 200mg once daily, 200mg twice daily and 400mg once daily doses of sotagliflozin, each administered in combination with standard metformin therapy over a 12 week treatment period. The primary efficacy endpoint under evaluation in the trial was the change in A1C from baseline to week 12. Secondary efficacy endpoints included percentage of patients achieving A1C levels of less than 7%, as well as changes in fasting plasma glucose levels, weight, blood pressure and triglyceride levels. Top-line data from the study showed that treatment with sotagliflozin demonstrated statistically significant benefits in the primary and multiple secondary endpoints. Patients in each of the 75mg once daily, 200mg once daily, 200mg twice daily and 400mg once daily sotagliflozin treatment arms had mean A1C reductions from baseline of 0.43, 0.52, 0.79 and 0.95 percent, respectively ($p<0.001$ for all treatment arms), while in patients randomized to placebo, A1C decreased by 0.09 percent. We also observed that patients treated with sotagliflozin showed significant reductions in body weight and blood pressure. Sotagliflozin was well tolerated and adverse events were generally mild to moderate, with the overall incidence of adverse events with sotagliflozin being similar to placebo.

We reported top-line data in October 2013 from a clinical trial evaluating the safety and tolerability of sotagliflozin and its effects on glycemic parameters associated with type 2 diabetes in patients with moderate renal impairment. The clinical trial enrolled 30 patients with type 2 diabetes and moderate to severe renal impairment in a randomized, double-blind, placebo-controlled study of a 400mg once daily dose of sotagliflozin over a seven-day treatment period. The primary efficacy endpoint under evaluation in the trial was the change in postprandial glucose from baseline to day seven, with secondary endpoints including a variety of glycemic control parameters. Top-line data from the study showed that treatment with sotagliflozin provided clinically meaningful and statistically significant reductions ($p<0.05$) in post-prandial glucose and produced significant elevations in GLP-1, a hormone involved in control of glucose and appetite. Sotagliflozin was well tolerated and adverse events were generally mild to moderate, with the overall incidence of adverse events with sotagliflozin being similar to placebo.

We previously completed a Phase 2a clinical trial in type 2 diabetes patients, in which sotagliflozin provided improvements in glycemic control, demonstrated statistically significant benefits in the primary and multiple secondary efficacy endpoints and demonstrated a favorable safety profile.

We do not intend to continue development of sotagliflozin in type 2 diabetes unless we enter into a collaboration partnership.

Other Clinical and Preclinical Development Programs

LX1033. LX1033 is an orally-delivered small molecule compound that is in development for the treatment of irritable bowel syndrome. LX1033 was internally generated by our medicinal chemists as an inhibitor of TPH, the same target as telotristat etiprate, but LX1033 is chemically distinct and was designed to reduce production of serotonin locally in the gastrointestinal tract without affecting serotonin synthesis elsewhere in the body.

We previously completed a Phase 2 clinical trial in patients suffering from diarrhea-predominant irritable bowel syndrome in which all treatment groups, including placebo, showed significant improvements in the primary efficacy endpoint over time. Such improvements in patients treated with LX1033 were not statistically significant relative to

those treated with placebo, but LX1033 reduced the production of plasma 5 HIAA significantly more than placebo, with the greatest reductions observed in patients treated with 500mg of LX1033 three times daily. LX1033 was well tolerated and adverse events were evenly distributed among all LX1033 and placebo treatment groups.

LX2931. LX2931 is an orally-delivered small molecule compound that is in development for the treatment of autoimmune disease. LX2931 was internally generated by our medicinal chemists to target sphingosine-1-phosphate lyase, or S1P lyase, an enzyme in the sphingosine-1 phosphate (S1P) pathway associated with the activity of lymphocytes. Lymphocytes are a cellular component and key driver of the immune system, and are involved in a number of autoimmune and inflammatory disorders. Our scientists discovered that mice lacking this enzyme have increased retention of immune cells in the thymus and spleen with a corresponding reduction in the deployment of T-cells and B-cells into the circulating blood.

We previously completed a Phase 2 clinical trial in rheumatoid arthritis patients who were also taking methotrexate, a standard therapy, in which patients treated with 150mg of LX2931 once daily showed an improvement in the primary efficacy endpoint which did not achieve statistical significance. Patients treated with 70mg and 110mg of LX2931 once daily did not indicate improvement relative to placebo. LX2931 was well tolerated, with no notable differences in adverse events observed between placebo and any of the treatment groups.

LX7101. LX7101 is a topically-delivered small molecule compound that is under evaluation as a potential treatment for glaucoma. LX7101 was internally generated by our medicinal chemists to target LIMK2, a kinase associated with the regulation of intraocular pressure, and is designed to lower intraocular pressure by enhancing the fluid outflow facility of the eye. Our scientists discovered that mice lacking LIMK2 exhibited lower intraocular pressure compared to normal mice. We previously completed a Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of LX7101 in glaucoma patients, as well as intraocular pressure.

Preclinical Development Programs. We have advanced small molecule compounds from a number of additional drug programs into various stages of preclinical development, including LX2761, an orally-delivered small molecule compound for the treatment of diabetes that is designed to inhibit SGLT1 locally in the gastrointestinal tract without any significant inhibition of SGLT2 in the kidney.

Drug Target Discoveries

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 preclinical development, originated from our own internal drug discovery efforts. These efforts were driven by a systematic, target 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.

Our Commercialization Strategy

We are working both independently and through strategic collaborations and alliances with third parties to capitalize on our drug target discoveries, and we intend to pursue the same strategy for our drug candidates in clinical development. Consistent with this approach, 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. We also seek to collaborate with other pharmaceutical and biotechnology companies, research institutes and academic institutions to capitalize on our drug target discoveries.

Strategic Collaborations

Ipsen. We entered into a license and collaboration agreement with Ipsen Pharma SAS in October 2014 under which we granted Ipsen an exclusive, royalty-bearing right and license to commercialize telotristat etiprate outside of the United States, Canada and Japan. We received a $23 million upfront payment under the agreement and we are eligible to receive up to approximately $30 million upon the achievement of specified regulatory and commercial launch milestones and up to €72 million upon the achievement of specified sales milestones. We are also entitled to tiered, escalating royalties ranging from low twenties to mid-thirties percentages of net sales of telotristat etiprate in the licensed territory, subject to a credit for Ipsen's payments to us for the manufacture and supply of such units of telotristat etiprate. Our receipt of these payments from Ipsen will trigger our obligation to make certain contingent payments to Symphony Icon Holdings LLC, or Holdings, pursuant to our prior arrangement with Holdings for the financing of the clinical development of telotristat etiprate.

Bristol-Myers Squibb. We established a drug discovery alliance with Bristol-Myers Squibb Company in December 2003 to discover, develop and commercialize small molecule drugs in the neuroscience field. Bristol-Myers Squibb extended the target discovery term of the alliance in May 2006. We initiated the alliance with a number of neuroscience drug discovery programs at various stages of development and used our gene knockout technologies to identify additional drug targets with promise in the neuroscience field. For those targets that were selected for the alliance, we and Bristol-Myers Squibb are working together, on an exclusive basis, to identify, characterize and carry out the preclinical development of small molecule drugs, and share equally both in the costs and in the work attributable to those efforts. As drugs resulting from the alliance enter clinical trials, Bristol-Myers Squibb will have the first option to assume full responsibility for clinical development and commercialization. We received $86 million in upfront payments and research funding under the agreement during the target discovery portion of the alliance, which expired in October 2009. In addition, we are entitled to receive clinical and regulatory milestone payments ranging, depending on the timing and extent of our efforts in the alliance, up to $76 million for each drug developed by Bristol-Myers Squibb under the alliance. We will also earn royalties on sales of drugs commercialized by Bristol-Myers Squibb under the alliance.

Genentech. We established a drug discovery alliance with Genentech, Inc. in December 2002 to discover novel therapeutic proteins and antibody targets. We and Genentech expanded the alliance in November 2005 for the advanced research, development and commercialization of new biotherapeutic drugs. Under the original alliance agreement, we used our target validation technologies to discover the functions of secreted proteins and potential antibody targets identified through Genentech's internal drug discovery research. In the expanded alliance, we conducted additional, advanced research on a broad subset of those proteins and targets. We have exclusive rights to develop and commercialize biotherapeutic drugs for two of these targets, while Genentech has exclusive rights to develop and commercialize biotherapeutic drugs for the other targets. We retain certain other rights to discoveries made in the alliance, including non-exclusive rights, along with Genentech, for the development and commercialization of small molecule drugs addressing the targets included in the alliance. We received $58 million in upfront payments, research funding and research milestone payments under the agreement during the research collaboration term, which expired in November 2008. In addition, we are entitled to receive clinical and regulatory milestone payments ranging, depending on the extent of our efforts in the alliance, up to $25 million for each drug target for which Genentech develops a biotherapeutic drug under the alliance. We will also earn royalties on sales of biotherapeutic drugs commercialized by Genentech under the alliance. Genentech is entitled to receive milestone payments and royalties on sales of biotherapeutic drugs which we develop or commercialize under the alliance.

Other Collaborations

We have established collaborations with a number of pharmaceutical and biotechnology companies, research institutes and academic institutions under which we have received fees in exchange for generating knockout mice for genes requested by the collaborator, providing phenotypic data with respect to such knockout mice or otherwise granting

access to some of our technologies and discoveries. In some cases, we remain eligible to receive milestone or royalty payments on the sale of mice and phenotypic data or on products that our collaborators discover or develop using our technology.

Our Executive Officers

Our executive officers and their ages and positions are listed below.

Name	Age	Position with the Company
Lonnel Coats	50	President and Chief Executive Officer and Director
Pablo Lapuerta, M.D.	51	Executive Vice President and Chief Medical Officer
Alan J. Main, Ph.D.	61	Executive Vice President, CMC and Supply Operations
Jeffrey L. Wade, J.D.	50	Executive Vice President, Corporate and Administrative Affairs and Chief Financial Officer
John P. Northcott	37	Vice President of Marketing, Commercial Strategy and Operations
James F. Tessmer	55	Vice President, Finance and Accounting

Lonnel Coats has been our president and chief executive officer and a director since July 2014. From 1996 through June 2014, Mr. Coats served in a series of leadership positions at Eisai Inc. and Eisai Corporation of North America, most recently as chief executive officer from 2010 to June 2014 and president and chief operating officer from 2004 to 2010. Prior to joining Eisai, Mr. Coats spent eight years with Janssen Pharmaceuticals, Inc., a division of Johnson & Johnson, where he held a variety of management and sales positions. Mr. Coats received his B.P.A. from Oakland University.

Pablo Lapuerta, M.D. has been our executive vice president and chief medical officer since February 2015. Dr. Lapuerta served as our executive vice president, safety, pharmacovigilance and medical affairs and chief medical officer from August 2014 until February 2015 and was our executive vice president, clinical development and chief medical officer from February 2013 until August 2014 and senior vice president, clinical development and chief medical officer from 2011 until February 2013. From 2009 through 2010, Dr. Lapuerta served as vice president at Bristol-Myers Squibb Company with responsibility for global development of an Alzheimer's disease drug candidate. From 2007 through 2009, Dr. Lapuerta was senior vice president, clinical strategy and chief medical officer of Cogentus Pharmaceuticals, Inc. and prior to that served in a variety of clinical development leadership roles at Bristol-Myers Squibb, where he worked for 11 years before joining Cogentus. He holds a B.A. in biology from Harvard College and an M.D. from Harvard Medical School.

Alan J. Main, Ph.D. has been our executive vice president, CMC and supply operations since February 2015. Dr. Main served as our executive vice president of pharmaceutical research from 2007 until February 2015 and was our senior vice president, Lexicon Pharmaceuticals from 2001 to 2007. Dr. Main was president and chief executive officer of Coelacanth Corporation, a leader in using proprietary chemistry technologies to rapidly discover new chemical entities for drug development, from 2000 until our acquisition of Coelacanth in 2001. Dr. Main was formerly senior vice president, U.S. Research at Novartis Pharmaceuticals Corporation, where he worked for 20 years before joining Coelacanth. Dr. Main holds a B.S. from the University of Aberdeen, Scotland and a Ph.D. in organic chemistry from the University of Liverpool, England and completed postdoctoral studies at the Woodward Research Institute.

Jeffrey L. Wade, J.D. has been our executive vice president, corporate and administrative affairs and chief financial officer since February 2015. Mr. Wade served as our executive vice president, corporate development and chief financial officer from May 2010 until February 2015 and was our executive vice president and general counsel from 2000 until May 2010 and senior vice president and chief financial officer from 1999 to 2000. From 1988 through 1998, Mr. Wade was a corporate securities and finance attorney with the law firm of Andrews & Kurth L.L.P., for the last two years as a partner, where he represented companies in the biotechnology, information technology and energy industries. Mr. Wade is a member of the board of directors of the Texas Healthcare and Bioscience Institute. He received his B.A. and J.D. from the University of Texas.

John P. Northcott has been our vice president of marketing, commercial strategy and operations since June 2013. From May 2011 through May 2013, Mr. Northcott served as International Business Leader for F. Hoffman-La Roche Ltd. with responsibility for the global strategy, commercialization and life cycle management of Avastin, an approved cancer drug product. From 2007 through May 2011, Mr. Northcott was Oncology Group Product Manager at Roche with responsibility for the commercialization of Avastin in the United States. Prior to joining Roche, Mr. Northcott spent five years in a variety of management and sales positions with Pfizer Inc., Pharmacia Corporation and Merck & Co. Mr. Northcott received his B.B.A. from St. Francis Xavier University.

James F. Tessmer has been our vice president, finance and accounting since November 2007 and previously served as our senior director of finance from 2004 to November 2007 and director of finance from 2001 to 2004. From January 1997 to 2001, Mr. Tessmer was assistant controller for Mariner Health Network, Inc. and prior to that served in a variety of financial and accounting management positions for HWC Distribution Corp. and American General Corporation. Mr. Tessmer is a certified public accountant and received his B.B.A. from the University of Wisconsin – Milwaukee and his M.B.A. from the University of Houston.

Patents and Proprietary Rights

We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that those rights are covered by valid and enforceable patents or are effectively maintained as trade secrets. Accordingly, patents and other proprietary rights are an essential element of our business. We own patent applications, and in some cases issued patents, covering each of our drug candidates in clinical development, including:

- worldwide patent applications that claim telotristat etiprate, or LX1032, and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, from which patents have granted in multiple jurisdictions, including ten in the United States;
- worldwide patent applications that claim sotagliflozin, or LX4211, and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, from which patents have granted in multiple jurisdictions, including four in the United States;
- worldwide patent applications that claim LX1033 and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, from which patents have granted in multiple jurisdictions, including ten in the United States;
- worldwide patent applications that claim LX2931 and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, from which patents have granted in multiple jurisdictions, including five in the United States; and
- worldwide patent applications that claim LX7101 and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, from which patents have granted in multiple jurisdictions, including two in the United States.

Additionally, we hold rights to a number of patents and patent applications under license agreements with third parties. Many of these licenses are nonexclusive, although some are exclusive in specified fields. Most of the licenses have terms that extend for the life of the licensed patents.

Patents extend for varying periods according to the date of patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The actual protection afforded by a patent, which can vary from country to country, depends on the type of patent, the scope of its coverage and the availability of legal remedies in the country. We have filed patent applications and hold issued patents covering each of our drug candidates in clinical development. No United States patent that has issued or may issue based on a patent application we have filed relating to one of our drug candidates in clinical development has a normal expiration date earlier than 2026.

All of our employees, consultants and advisors are required to execute a proprietary information agreement upon the commencement of employment or consultation. In general, the agreement provides that all inventions conceived by

the employee or consultant, and all confidential information developed or made known to the individual during the term of the agreement, shall be our exclusive property and shall be kept confidential, with disclosure to third parties allowed only in specified circumstances. We cannot assure you, however, that these agreements will provide useful protection of our proprietary information in the event of unauthorized use or disclosure of such information.

Our patent and intellectual property rights are subject to certain rights and uncertainties. See “Risks Related to Our Intellectual Property” under “Item 1A. Risk Factors.”

Competition

The biotechnology and pharmaceutical industries are highly competitive and characterized by rapid technological change. We face significant competition in each of the aspects of our business from other pharmaceutical and biotechnology companies. Many of our competitors have substantially greater research, development and commercialization capabilities and financial, scientific, marketing and human resources than we do. As a result, our competitors may succeed in developing products earlier than we do, obtaining approvals from the FDA or other regulatory agencies for those products more rapidly than we do, developing products that are more effective than those we propose to develop or commercializing products more effectively and profitably than we do. Similarly, our collaborators face similar competition from other competitors who may succeed in developing products more quickly, developing products that are more effective than those developed by our collaborators or commercialize products more effectively and profitably than our collaborators. Any products that we or our collaborators may develop or discover are likely to be in highly competitive markets.

The competition for our drug candidates includes both marketed products and drug candidates that are being developed by others, including drug candidates that are currently in a more advanced stage of clinical development or commercialization than are our own drug candidates. These competitive marketed products and drug candidates include compounds that employ different mechanisms of action in addressing diseases and conditions for which we are developing our own drug candidates and, in some cases such as sotagliflozin, that employ the same or similar mechanisms of action.

We believe that our ability to successfully compete with these potentially competitive drug candidates and other competitive products currently on the market will depend on, among other things:

- the efficacy, safety and reliability of our drug candidates;
- our ability, and the ability of our collaborators, to complete nonclinical testing and clinical development and obtain regulatory approvals for our drug candidates;
- the timing and scope of regulatory approvals for our drug candidates;
- our ability, and the ability of our collaborators, to obtain product acceptance by physicians and other health care providers and reimbursement for product use in approved indications;
- our ability, and the ability of our collaborators, to manufacture and sell commercial quantities of our products;
- the skills of our employees and our ability to recruit and retain skilled employees;
- protection of our intellectual property; and
- the availability of substantial capital resources to fund development and commercialization activities.

Government Regulation

Regulation of Pharmaceutical Products

The development, manufacture and sale of any products developed by us or our collaborators will be subject to extensive regulation by United States and foreign governmental authorities, including federal, state and local authorities. In the United States, new drugs are subject to regulation under the Federal Food, Drug and Cosmetic Act and the regulations promulgated thereunder, or the FDC Act, and biologic products are subject to regulation both under certain provisions of the FDC Act and under the Public Health Services Act and the regulations promulgated thereunder, or the PHS Act. The FDA regulates, among other things, the development, preclinical and clinical testing, manufacture, safety, efficacy, record keeping, reporting, labeling, storage, approval, advertising, promotion, sale, distribution and export of small molecule and biotherapeutic drugs.

The standard process required by the FDA before a drug candidate may be marketed in the United States includes:

- nonclinical laboratory and animal tests performed under the FDA's current Good Laboratory Practices regulations;
- submission to the FDA of an Investigational New Drug application, or IND, which must become effective before human clinical trials may commence;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the drug candidate for its intended use;
- for drug candidates regulated as small molecule drugs, submission of a New Drug Application, or NDA, and, for drug candidates regulated as biotherapeutic drugs, submission of a Biologic License Application, or BLA, with the FDA; and
- FDA approval of the NDA or BLA prior to any commercial sale or shipment of the product.

This process for the testing and approval of drug candidates requires substantial time, effort and financial resources. Preclinical development of a drug candidate can take from one to several years to complete, with no guarantee that an IND based on those studies will become effective to even permit clinical testing to begin. Before commencing the first clinical trial of a drug candidate in the United States, we must submit an IND to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions about the conduct of the clinical trial. In such a case, we and the FDA must resolve any outstanding concerns before the clinical trial may begin. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development, and the FDA must grant permission for each clinical trial to start and continue. Further, an independent institutional review board for each medical center proposing to participate in the clinical trial must review and approve the plan for any clinical trial before it commences at that center. Regulatory authorities or an institutional review board or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

For purposes of NDA or BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap.

- Phase 1 clinical trials are conducted in a limited number of healthy human volunteers or, in some cases, patients, to evaluate the safety, dosage tolerance, absorption, metabolism, distribution and excretion of the drug candidate;
- Phase 2 clinical trials are conducted in groups of patients afflicted with a specified disease or condition to obtain preliminary data regarding efficacy as well as to further evaluate safety and optimize dosing of the drug candidate; and
- Phase 3 clinical trials are conducted in larger patient populations at multiple clinical trial sites to obtain statistically significant evidence of the efficacy of the drug candidate for its intended use and to further test for safety in an expanded patient population.

In addition, the FDA may require, or companies may pursue, additional clinical trials after a product is approved. These so-called Phase 4 studies may be made a condition to be satisfied after a drug receives approval.

Completion of the clinical trials necessary for an NDA or BLA submission typically takes many years, with the actual time required varying substantially based on, among other things, the nature and complexity of the drug candidate and of the disease or condition. Success in earlier-stage clinical trials does not ensure success in later-stage clinical trials. Furthermore, data obtained from clinical activities is not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent proceeding with further clinical trials, filing or acceptance of an NDA or BLA, or obtaining marketing approval.

After completion of clinical trials, FDA approval of an NDA or BLA must be obtained before a new drug may be marketed in the United States. An NDA or BLA, depending on the submission, must contain, among other things, information on chemistry, manufacturing controls and potency and purity, non-clinical pharmacology and toxicology, human pharmacokinetics and bioavailability and clinical data. There can be no assurance that the FDA will accept an NDA or BLA for filing and, even if filed, that approval will be granted. Among other things, the FDA reviews an NDA to determine whether a product is safe and effective for its intended use and a BLA to determine whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency. The FDA may deny approval of an NDA or BLA if the applicable regulatory criteria are not satisfied, or it may require additional clinical data or an additional pivotal Phase 3 clinical trial. Even if such data are submitted, the FDA may ultimately decide that the NDA or BLA does not satisfy the criteria for approval. Once issued, the FDA may withdraw product approval if ongoing regulatory standards are not met or if safety problems occur after the product reaches the market. In addition, the FDA may require testing and surveillance programs to monitor the effect of approved products which have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs. Limited indications for use or other conditions could also be placed on any approvals that could restrict the commercial applications of a product or impose costly procedures in connection with the commercialization or use of the product.

In addition to obtaining FDA approval for each product, each drug manufacturing establishment must be inspected and approved by the FDA. All manufacturing establishments are subject to inspections by the FDA and by other federal, state and local agencies and must comply with current Good Manufacturing Practices requirements. Non-compliance with these requirements can result in, among other things, total or partial suspension of production, failure of the government to grant approval for marketing and withdrawal, suspension or revocation of marketing approvals.

Once the FDA approves a product, a manufacturer must provide certain updated safety and efficacy information. Product changes as well as certain changes in a manufacturing process or facility would necessitate additional FDA review and approval. Other post-approval changes may also necessitate further FDA review and approval. Additionally, a manufacturer must meet other requirements including those related to adverse event reporting and record keeping.

The FDA closely regulates the marketing and promotion of drugs. A company can make only those claims relating to safety and efficacy that are approved by the FDA. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties.

Violations of the FDC Act, the PHS Act or regulatory requirements may result in agency enforcement action, including voluntary or mandatory recall, license suspension or revocation, product seizure, fines, injunctions and civil or criminal penalties.

In addition to regulatory approvals that must be obtained in the United States, drugs are also subject to regulatory approval in other countries in which they are marketed. The conduct of clinical trials of drugs in countries other than the United States is likewise subject to regulatory oversight in such countries. The requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary widely from country to country. No action can be taken to market any drug in a country until the regulatory authorities in that country have approved an

appropriate application. FDA approval does not assure approval by other regulatory authorities. The current approval process varies from country to country, and the time spent in gaining approval varies from that required for FDA approval. In some countries, the sale price of a drug or biologic product must also be approved. The pricing review period often begins after marketing approval is granted. Even if a foreign regulatory authority approves a drug, it may not approve satisfactory prices for the product.

Other Regulations

In addition to the foregoing, our business is subject to regulation under various state and federal environmental laws, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in and wastes generated by our operations. We believe that we are in material compliance with applicable environmental laws and that our continued compliance with these laws will not have a material adverse effect on our business. We cannot predict, however, whether new regulatory restrictions will be imposed by state or federal regulators and agencies or whether existing laws and regulations will adversely affect us in the future.

Research and Development Expenses

In 2014, 2013 and 2012, respectively, we incurred expenses of $89.3 million, $89.7 million and $82.6 million in company-sponsored as well as collaborative research and development activities, including $4.0 million, $4.4 million and $3.7 million of stock-based compensation expense in 2014, 2013 and 2012, respectively.

Employees and Consultants

As of February 27, 2015, we employed 106 persons, of whom 24 hold M.D. or Ph.D. degrees and another 21 hold other advanced degrees. We believe that our relationship with our employees is good.

Item 1A. Risk Factors

The following risks and uncertainties are important factors that could cause actual results or events to differ materially from those indicated by forward-looking statements. The factors described below are not the only ones we face and additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations.

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 December 31, 2014, we had $339.3 million in cash, cash equivalents and investments. 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 (a) 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, (b) a companion Phase 3 clinical trial of telotristat etiprate to study safety and 5-HIAA in a separate patient population, with a targeted enrollment of approximately 60 patients, (c) a Phase 2 clinical trial of sotagliflozin in a younger adult type 1 diabetes population and (d) three concurrent Phase 3 clinical trials for sotagliflozin in type 1 diabetes, which we expect to enroll an aggregate of approximately 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 and clinical 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.

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 $100.3 million for the year ended December 31, 2014, $104.1 million for the year ended December 31, 2013 and $110.2 million for the year ended December 31, 2012. As of December 31, 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 amount 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 technology licenses, 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 substantial indebtedness that may limit cash flow available to invest in the ongoing needs of our business.

We have incurred $107.7 million of indebtedness and could in the future incur additional indebtedness beyond such amount. We are not restricted under the terms of our existing debt instruments 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 the notes evidencing our existing indebtedness upon a fundamental change, and our future debt may contain limitations on our ability to repurchase the notes. Holders of the notes evidencing our existing indebtedness 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 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 sotaglifozin, 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 sotaglifozin 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 sotaglifozin. 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 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.

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;

- 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. 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.

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 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 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 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, L.P., Invus C.V. and their 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 59.8% 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 the notes evidencing our current indebtedness 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 the notes evidencing our current indebtedness 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 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.