

Xenon Pharmaceuticals Inc.  
Form 10-K  
March 08, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934  
For the fiscal year ended December 31, 2015

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: 001-36687

XENON PHARMACEUTICALS INC.

(Exact Name of Registrant as Specified in its Charter)

Canada 98-0661854  
(State or other jurisdiction (I.R.S. Employer

of incorporation or organization) Identification Number)

200 – 3650 Gilmore Way

Burnaby, British Columbia V5G 4W8

Canada

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(Address of Principal Executive Offices, including zip code)

(Registrant's Telephone Number, Including Area Code): (604) 484-3300

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

Title of Each Class	Name of Exchange on Which Registered
Common Shares, no par value per share	The NASDAQ Stock Market LLC  (The NASDAQ Global 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. Yes  No

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

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  No

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 (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes  No

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 the 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.

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 Exchange Act.:

Large accelerated filer  Accelerated filer

Non-accelerated filer  Smaller reporting company

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  No

The aggregate market value of the voting and non-voting common shares held by non-affiliates of the registrant, based on the closing sale price of the registrant's common shares on the last business day of its most recently completed second fiscal quarter, as reported on The NASDAQ Global Market, was approximately \$141 million. Common shares

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held by each executive officer and director and by each other person who may be deemed to be an affiliate of the registrant, have been excluded from this computation. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of outstanding common shares of the registrant, no par value per share, as of March 4, 2016 was 14,401,582.

### DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement to be filed with the Securities and Exchange Commission in connection with the registrant's 2016 Annual Meeting of Shareholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this Form 10-K. Such Proxy Statement will be filed with the Securities and Exchange Commission not later than 120 days following the end of the registrant's fiscal year ended December 31, 2015.

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XENON PHARMACEUTICALS INC.

FORM 10-K

For the Fiscal Year Ended December 31, 2015

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## PART I

### Forward-Looking Statements

Certain statements contained in this Annual Report on Form 10-K may constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended and Canadian securities laws. The words or phrases “would be,” “will allow,” “intends to,” “may,” “believe,” “plan,” “will likely result,” “are expected to,” “will continue,” “is anticipated,” “estimate,” “project,” or similar expressions or the negative of such words or phrases, are intended to identify “forward-looking statements.” You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other “forward-looking” information. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements include, but are not limited to:

- our ability to identify additional products or product candidates using our Extreme Genetics discovery platform;
- the initiation, timing, cost, progress and success of our research and development programs, preclinical studies and clinical trials;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- our ability to recruit sufficient numbers of patients for our current and future clinical trials for orphan or more common indications;
- our ability to achieve profitability;
- our ability to obtain funding for our operations, including research funding;
- our ability to receive milestones, royalties and sublicensing fees under our collaborations, and the timing of such payments;
- the implementation of our business model and strategic plans;
- our ability to develop and commercialize product candidates for orphan and niche indications independently;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our ability to find families to support our Extreme Genetics discovery platform;
- our ability to discover genes and drug targets;
- our ability to protect our intellectual property and operate our business without infringing upon the intellectual property rights of others;
- our expectations regarding federal, state and foreign regulatory requirements;
- the therapeutic benefits, effectiveness and safety of our product candidates;
- the accuracy of our estimates of the size and characteristics of the markets that may be addressed by our products and product candidates;
- the rate and degree of market acceptance and clinical utility of Glybera and future products, if any;
- the timing of, and our and our collaborators’ ability to obtain and maintain regulatory approvals for our product candidates;
- our ability to maintain and establish collaborations;
- our expectations regarding market risk, including interest rate changes and foreign currency fluctuations;
- our belief in the sufficiency of our cash flows to meet our needs for at least the next 12 to 24 months;
- our ability to engage and retain the employees required to grow our business;
- our future financial performance and projected expenditures;
- developments relating to our competitors and our industry, including the success of competing therapies that are or become available; and
- estimates of our expenses, future revenue, capital requirements and our needs for additional financing.

These forward-looking statements are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those discussed in this report in Part I, Item 1A — “Risk Factors,” and elsewhere in this report. Forward-looking statements are based on our management’s beliefs and assumptions and on information currently available to our management. These statements, like all statements in this report, speak only as of their date, and we undertake no obligation to update or revise these statements in light of future developments. In this report, “we,” “our,” “us,” “Xenon,” and “the Company” refer to Xenon Pharmaceuticals Inc. Unless otherwise noted, all dollar amounts in this report are expressed in United States dollars.

This Annual Report on Form 10-K includes our trademarks and registered trademarks, including the Xenon logo, “Extreme Genetics” and other trademarks or service marks of Xenon. Each other trademark, trade name or service mark appearing in this Annual Report on Form 10-K belongs to its holder.

## Item 1. Business

### Overview

We are a clinical-stage biopharmaceutical company discovering and developing a pipeline of differentiated therapeutics for orphan indications that we intend to commercialize on our own, and for larger market indications that we intend to partner with global pharmaceutical companies. We have built a core enabling discovery platform for the discovery of validated drug targets by studying rare human diseases with extreme traits, including diseases caused by mutations in ion channels, known as channelopathies. We have an integrated platform that includes in-house capabilities for human genetics, small molecule drug discovery, as well as preclinical and clinical development.

Our pharmaceutical partners include Teva Pharmaceutical Industries, Ltd., or Teva (through its subsidiary, Ivax International GmbH), Genentech, Inc., or Genentech, and Merck & Co., Inc., or Merck (through its affiliate, Essex Chemie AG). Our pharmaceutical collaborations have generated in aggregate over \$155.0 million in non-equity funding to date with the potential to provide us with over \$1.0 billion in future milestone payments, as well as royalties and co-promotion income on product sales.

Our business was founded on our proprietary discovery platform, which we refer to as Extreme Genetics. Extreme Genetics involves the study of families where individuals exhibit inherited severe traits, or phenotypes. By identifying and characterizing single-gene defects responsible for these phenotypes, we gain insights into human disease biology to better select targets for therapeutic intervention. We believe that our Extreme Genetics discovery platform enhances the likelihood of discovering a drug target that has a major effect in humans. From these discoveries, we can gain an improved understanding of how a drug that modulates the target might act when given to a human.

Our Extreme Genetics discovery platform has yielded the first approved gene therapy product in the European Union, or the EU, and a broad proprietary development pipeline and multiple pharmaceutical partnerships, which include:

- Glybera, developed by our licensee uniQure Biopharma B.V., or uniQure, the first, and currently the only, gene therapy product approved in the EU for the treatment of the orphan disorder lipoprotein lipase deficiency, or LPLD. The first patient treated with Glybera as a commercially-available gene therapy was announced by uniQure in November 2015 and enabled by its commercialization partner in the EU, Chiesi Farmaceutici S.p.A., or Chiesi, which has sole control over commercialization in the EU;
- TV-45070 (formerly XEN402), a product candidate being developed in collaboration with Teva for the treatment of pain. Teva is currently conducting a randomized, double-blind, placebo-controlled Phase 2b clinical trial in patients with post-herpetic neuralgia, or PHN, with results expected in the second half of 2016. TV-45070 is a topically applied small-molecule inhibitor of the sodium channel Nav1.7 and other sodium channels, including those that are expressed in the pain-sensing peripheral nervous system;

- GDC-0276 and GDC-0310, which are both oral, selective Nav1.7 small-molecule inhibitors being developed in collaboration with Genentech for the potential treatment of pain. Phase 1 clinical trials for GDC-0276 and GDC-0310 are ongoing, and pending a full assessment of the results, Genentech intends to initiate a Phase 2 clinical trial in 2016. Xenon and Genentech also have an active research collaboration focused on other orally selective small molecule inhibitors of Nav1.7;
- XEN801, a stearoyl Co-A desaturase-1, or SCD1, inhibitor being developed for the treatment of acne. SCD1 is an enzyme involved in lipid synthesis that is expressed in sebaceous glands in the skin. We have completed a Phase 1 clinical trial for XEN801 and initiated a Phase 2 clinical trial in February 2016 in patients with moderate to severe facial acne. We anticipate topline results in the fourth quarter of 2016; and

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- additional proprietary preclinical programs, including a Nav1.6 sodium channel inhibitor for the treatment of rare childhood epilepsy disorders, such as Dravet Syndrome, or DS, an orphan disease of severe childhood epilepsy. We expect to identify a development candidate in 2016 and file an investigational new drug, or IND, application for our Nav1.6 inhibitor in the first half of 2017.

### Our Strategy

Our goal is to build a self-sustaining, fully-integrated and profitable company that discovers, develops and commercializes innovative therapeutics, including novel selective ion channel inhibitors, by applying our expertise in the genetics of rare human diseases.

Since our inception, we believe we have operated in a capital-efficient manner to build our capabilities and assets through phased growth, expansion and value creation. Prior to our November 2014 initial public offering and concurrent private placement, our last equity financing was in 2006. From 2006 to November 2014, we funded our operations and expanded our platform, product pipeline and infrastructure through a strategy which combined the deployment of our own resources and the establishment of broadly enabling and well-structured pharmaceutical partnerships with industry leaders.

Our strategy includes:

- Expanding our pipeline and advancing multiple discovery and development programs, focusing on orphan and niche disease market opportunities that we can independently develop and commercialize ourselves.
- Selectively establishing additional partnerships enabling us to access large commercial indications while leveraging the benefits of those collaborations to expand our internal capabilities.
- Further leveraging our discovery platform and insights into disease biology to identify novel targets and develop next-generation products.

### Our Extreme Genetics Discovery Platform

Despite advances in medical sciences and the pharmaceutical industry's understanding of diseases, research and development productivity in the industry has declined over the years. We believe that a contributor to this problem is the industry's reliance on drug discovery approaches that are sometimes based on targets that do not necessarily have a major biological effect in humans. Consequently, it is fairly common for a pharmaceutical company to invest substantial time, resources and funds into drug development only to realize in late-stage clinical trials that a product candidate may be directed to a target that is either not biologically relevant to the disease or that may have diverse functions or effects in humans, thereby leading to poor efficacy or safety.

Our Extreme Genetics discovery platform enables us to identify drug targets that may be more biologically relevant in humans. Our platform is built on the foundation of identifying and studying rare individuals and families with severe phenotypes to discover single-gene defects that have major biological effects in humans. By studying these individuals and families with severe phenotypes, we can obtain critical insights into the genes underlying these diseases and their related biology to develop promising product candidates. We therefore are able to initiate our drug discovery efforts with the advantage of having a greater understanding of the role of the drug target in human disease.

The selection of suitable families with rare phenotypes is integral to our successful identification of single-gene defects. Such families are rare and dispersed throughout the world, which makes accessing and studying such families a challenge. We have developed internal clinical genetics expertise allowing us to identify and access rare families. To date, we have established a global network that has included more than 30 clinical collaborations in multiple countries. We collect DNA and detailed clinical information from the selected families to which we then apply our in-house genetics, molecular biology and bioinformatics capabilities to identify the single-gene defect. Using these genetic insights, we apply our in-house, small-molecule expertise as well as access other therapeutic modalities, with



the goal of developing novel medicines.

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Our reliance on our Extreme Genetics discovery platform for target selection differs from other target selection methods commonly employed in the industry, such as in vitro cell biology and screening, tissue and differential expression studies, in vitro and animal based pharmacology and the use of animal models, such as gene knock-outs or animal transgenics. Some companies, however, do use human genetics to varying degrees to assist with target identification, such as approaches where larger populations of patients and controls are studied to define associations where a disease and single nucleotide polymorphisms, or SNPs, in certain genes are linked. While SNP associations allow the identifications of genes that show an association with a disease or may increase risk of disease, such associations differ from our Extreme Genetics discovery platform since they do not discover genes that are determinant or causal of a disease. By studying families with rare diseases where individuals present with severe phenotypes, we seek to isolate the genetic cause of such diseases. We then use this causal information as our primary methodology underlying our target discovery and selection.

The key components of our Extreme Genetics discovery platform include:

- clinical geneticists and genetic counselors with a deep understanding of clinical phenotypes. These experts identify the rare genetic disorders with severe phenotypes that we study;
  - years of experience and extensive know-how in successfully navigating through regulations in multiple countries in order to obtain the approvals necessary to collect and use detailed clinical information and DNA samples from individuals and families with severe phenotypes;
  - internal capabilities in genome sequencing, molecular biology and bioinformatics to enable identification of single-gene defects and validation of these as potential drug targets;
  - expertise in small-molecule drug discovery to design promising product candidates that effectively modulate the identified drug targets. Our drug discovery capabilities include medicinal and synthetic chemistry, assay development and in vitro and in vivo pharmacology; and
  - an established global network that has included more than 30 clinical collaborators in multiple countries, and which has provided us with access to rare individuals and families with severe phenotypes dispersed throughout the world.
- In addition, Xenon has built upon our global network by developing a new direct-to-patient web-based recruitment approach for identifying patients with rare or extreme phenotypes. By leveraging social media tools and allowing potential participants to directly access research studies online, we have successfully broadened the recruitment of participants for several of our research studies.

#### Focus on Human Channelopathies

A significant focus of our Extreme Genetics discovery platform has been human channelopathies, enabling us to develop strong capabilities in small molecule ion channel drug discovery. Our ion channel discovery capability is founded upon our understanding of the genetics of channelopathies combined with our proprietary biology and medicinal chemistry assets and know-how. We identified new binding sites on ion channels which, in turn, led to the discovery of highly-selective voltage-gated ion channel inhibitors which may have safety and efficacy advantages over non-selective inhibitors.

While the pharmaceutical industry has shown significant interest in channelopathies, a general inability to target ion channels selectively with a pharmaceutical agent has been a limitation to the development of effective therapeutics. We believe we have developed a core competence in developing highly-selective small-molecule ion channel inhibitors, and we believe we can use this know-how to develop a pipeline of novel ion channel inhibitors for diseases in areas of high unmet medical need.

For example, we discovered that deficiency of the voltage-gated sodium channel Nav1.7 is present in the rare human disease called congenital indifference to pain, or CIP. Individuals with CIP are unable to feel pain. This relationship indicated that Nav1.7 may be a key mechanism for the development of novel analgesics. We are pursuing this

mechanism in separate partnerships with Teva and with Genentech.

Similarly, with our collaborators from McGill University, we identified the genetic link between rare human epilepsies and mutations in the Nav1.1 sodium channel. These genetic epilepsy discoveries helped to define our therapeutic selective ion channel strategy for DS and other rare childhood epilepsies. We believe that our Extreme Genetics discovery platform provides the opportunity to validate additional ion channel targets for both prevalent and orphan indications.

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## Our Pipeline

Our pipeline is summarized in the following figure, which shows both our partnered programs and our own proprietary product candidates:

## Our Partnered Programs

### Glybera (alipogene tiparvovec): A Gene Therapy for the Orphan Disease LPLD

Glybera is a gene therapy product approved in the EU in October 2012 for the treatment of a subset of patients with the orphan lipid disorder lipoprotein lipase deficiency, or LPLD. Specifically, it is intended to treat LPLD in patients with severe or multiple pancreatitis attacks, despite dietary fat restrictions. LPLD is a severe metabolic disease of inadequate lipid metabolism, resulting in pancreatitis and in some cases, death. In collaboration with the University of British Columbia, or UBC, we demonstrated that humans with a variant of the lipoprotein lipase, or LPL, gene called LPL<sup>S447X</sup> resulted in increased LPL enzyme activity leading to reduced triglyceride levels. Under our sublicense and research agreement with uniQure, we collaborated with uniQure and UBC on preclinical activities, and thereafter uniQure developed a LPL gene therapy product, Glybera, which contains the LPL<sup>S447X</sup> variant. We believe that the introduction of the therapeutic LPL<sup>S447X</sup> gene through administration of Glybera provides a clinical benefit for LPLD patients.

Glybera is the first product whose active ingredient was derived from our platform to receive commercial approval and is the first gene therapy product to be approved in the EU. The goal of Glybera therapy is to treat LPLD in order to achieve sustained improvement of clearance of triglyceride-rich lipid particles known as chylomicrons, and to significantly reduce the risk of pancreatitis attacks in patients suffering from multiple recurrent pancreatitis and abdominal pain events.

## About LPLD

Familial LPLD is a rare autosomal-recessive disorder of lipoprotein metabolism. LPLD is characterized by severe hypertriglyceridemia caused by the absence of LPL activity, and, as a consequence, certain triglyceride-rich lipoproteins accumulate in the plasma. The population frequency of LPLD in the U.S. has been reported to be approximately one in a million individuals by the National Library of Medicine.

LPLD typically manifests early in childhood, with repeated episodes of abdominal pain and acute pancreatitis that can be life-threatening. There is currently no approved gene therapy for LPLD in the U.S. The current management of LPLD consists of strict adherence to an extremely low-fat diet, but compliance with such a diet is challenging. Lipid-lowering drugs are generally not effective for treating LPLD. We believe effective therapeutic strategies are therefore needed for this condition.

## About LPL<sup>S447X</sup>

Together with our collaborators at UBC and using our Extreme Genetics discovery platform, we demonstrated that the LPL<sup>S447X</sup> variant resulted in reduced triglyceride levels in humans, as this single-gene defect results in elevated LPL enzyme activity, and we further demonstrated that LPL<sup>S447X</sup> in an adenovirus gene therapy could treat hypertriglyceridemia in animal models of LPLD.

## Clinical Development of Glybera

In a scientific publication, a single dose of Glybera was well-tolerated with no material safety concerns and was demonstrated to reduce the incidence of acute pancreatitis and abdominal pain events over the two-year study period.

## Commercialization of Glybera

In 2012, Glybera was approved in the EU for the orphan disorder LPLD to treat patients with severe or multiple pancreatitis attacks. In July 2013, uniQure announced that it had entered into a partnership with Chiesi for the commercialization of Glybera in the EU and more than a dozen other countries including Brazil, China, Mexico and Russia. Glybera has received both fast-track and orphan drug designations for the treatment of LPLD in both the EU and the U.S. The first patient treated with Glybera as a commercially-available gene therapy in the EU was announced by uniQure in November 2015. Although commercial sales of Glybera have now commenced, we do not expect to receive significant revenue in the near-term from these sales. uniQure also disclosed in November 2015 that it will not pursue U.S. regulatory approval of Glybera in order to maintain its focus on three core therapeutic areas. uniQure has announced that it will not provide additional guidance regarding commercialization progress for Glybera. For a more detailed description of the terms of our agreement with uniQure for Glybera, see “—Strategic Alliances” below.

## TV-45070: A Small Molecule for the Treatment of Pain

TV-45070 (formerly XEN402) is a small-molecule inhibitor of the sodium channel Nav1.7 and other sodium channels, including those that are expressed in the pain-sensing peripheral nervous system. TV-45070 has potential application in neuropathic pain mediated by damage, dysfunction, or injury of nerves. TV-45070 is partnered with Teva. Using a topical ointment formulation of TV-45070, Teva is currently conducting a randomized, double-blind, placebo-controlled Phase 2b clinical trial in patients with PHN with results expected in the second half of 2016. Pursuant to the terms of our agreement with Teva, Teva is obligated to complete one additional Phase 2 or later stage clinical trial.

We selected Nav1.7 as a drug target for pain after we discovered that the Nav1.7 protein is deficient in the rare human disease, CIP, where humans suffering from CIP are unable to feel pain. We have observed promising evidence of activity for TV-45070 in four Phase 2 proof-of-concept clinical trials, including two trials in the orphan disease erythromelalgia, or EM, one trial in PHN and one trial in dental pain, a form of nociceptive pain. In December 2012, we entered into a collaborative development and license agreement with Teva through its subsidiary Ivax, pursuant to which we granted Teva an exclusive worldwide license to develop and commercialize TV-45070. For a more detailed description of the terms of our agreement with Teva, see “—Strategic Alliances” below. Prior to our entry into a collaborative development and license agreement with Teva, we submitted INDs to the FDA for oral TV-45070 for the indication of dental pain (July 2009) and topical TV-45070 for the indication of acute and chronic pain, including neuropathic and inflammatory pain (July 2010). Teva submitted an IND to the FDA for topical TV-45070 for the symptomatic treatment of osteoarthritis, or OA (November 2013).

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## Discovery of TV-45070 and Mechanism of Action

Using our Extreme Genetics discovery platform, we discovered Nav1.7 by studying families with the rare disorder CIP. Patients with CIP are unable to feel pain for painful events including fractures, childbirth, osteomyelitis, severe burns, ulcers, wounds and tooth abscesses. Based on this severe phenotype of absence of pain in humans with CIP, we predicted that the single-gene defect causing CIP could define an important novel human drug target for treating pain. We showed that defects in the CIP gene result in deficiency of the sodium channel Nav1.7.

Nav1.7 is highly expressed in peripheral nerves and transmits pain signals. We believe that inhibition of Nav1.7 may reduce these pain signals. TV-45070 was designed to be a non-selective small-molecule inhibitor of Nav1.7 such that it also can inhibit additional sodium channels, including those that we believe play a role in pain signaling. We believe this mixed sodium channel inhibition may enhance the potential efficacy of TV-45070 in chronic pain. TV-45070 is currently being developed as a topical product as its chemical properties are favorable for topical administration, including high local skin and underlying tissue concentrations with low plasma levels. With these properties, we believe we can target the site of generation of peripherally-based pain without unnecessarily exposing other tissues to significant levels of this compound. This is especially true for the central nervous system where we might expect to observe side-effects when multiple sodium channels are inhibited, such as sleepiness, nausea, and dizziness. We have demonstrated efficacy with this compound in multiple animal models for pain including both nociceptive and neuropathic pain models. The broad sodium channel inhibition of TV-45070 is in contrast to our selective inhibitors licensed to Genentech, which are selective for Nav1.7 and are being developed as oral formulations.

## Clinical Development of TV-45070

We are collaborating with Teva on the development of topical TV-45070. Topical and oral formulations of TV-45070 have been studied in Phase 1 clinical trials in healthy volunteers, four Phase 2 proof-of-concept clinical trials, a Phase 2b clinical trial in OA of the knee, and an ongoing Phase 2b clinical trial in PHN, with data expected in the second half of 2016. Pursuant to the terms of our agreement with Teva, they are obligated to complete one additional Phase 2 or later stage clinical trial.

### TV-45070 Phase 1 Clinical Trials

In a topical Phase 1 study, 20 healthy volunteers were dosed once daily for 21 days with 4% and 8% ointment, placebo, a positive control and a 0.9% saline negative control. Topical TV-45070 was generally well tolerated with no clinically meaningful difference observed between cumulative skin irritation scores for 4% and 8% ointment, placebo and the negative saline control. The positive control as expected did show greater skin irritation; there were no serious adverse events, or SAEs, or deaths in this study. All adverse events were moderate or mild in severity with the majority of adverse events related to local skin reactions from the occlusive tape dressings. The most frequently reported adverse events which were not local skin reactions were headache, dizziness, fatigue, and oropharyngeal pain. Importantly the average plasma concentrations of TV-45070 were low and, as would be expected, central nervous system side effects were of low incidence.

To better understand the systemic side effect profile of TV-45070, the drug was also dosed in Phase 1 single and multiple ascending dose studies using a simple liquid-filled capsule for oral administration. The single-ascending dose, or SAD, study was carried out in 38 healthy volunteers dosed up to 800 mg. The multi-ascending dose, or MAD, study was performed in 32 healthy volunteers who were dosed up to 400 mg twice daily for 5.5 days. The maximal tolerated dose, or MTD, for SAD study was 500 mg and dose-limiting toxicity included dizziness and drowsiness observed for the 800 mg single dose, which we believe indicates inhibition of central nervous system expressed sodium channels. The MTD in the MAD study was not achieved and occasional short-lived adverse events of mild to moderate dizziness and drowsiness were reported by some subjects for the 400 mg twice daily dose.

TV-45070 Phase 2 Proof-of-Concept Clinical Trials

Based on the potential broad utility of TV-45070, prior to our collaboration with Teva, we conducted four Phase 2 proof-of-concept trials to explore the potential of TV-45070 as a treatment for both nociceptive and neuropathic pain, as well as providing evidence that TV-45070 can block the pain signaling mediated by Nav1.7. These trials included: (1) an oral Phase 2 clinical trial in third molar tooth extraction; (2) an oral Phase 2 clinical trial in the orphan indication EM; (3) a topical Phase 2 clinical trial in EM; and, (4) a topical Phase 2 clinical trial in PHN.



We conducted a trial for third molar tooth extraction, which is an established acute inflammatory pain model. We performed a randomized, double-blind, placebo-controlled, Phase 2 proof-of-concept trial in 61 healthy male subjects, of which, 41 subjects received a single oral 500 mg dose of TV-45070 and 20 subjects received placebo. Oral TV-45070 was well-tolerated with no SAEs. The most frequently reported adverse events were nausea, dizziness, headache and drowsiness, which were mild or moderate in intensity. The primary and all secondary endpoints showed consistent trends in favor of reduced pain for TV-45070 versus placebo. The primary efficacy endpoint was the change in total pain relief at six hours post-dose. TV-45070-treated subjects experienced greater pain relief compared to subjects who received placebo ( $p=0.171$ ), although the difference did not achieve the pre-defined statistical significance for the trial of  $p=0.1$ . In a post-hoc analysis, a significantly increased proportion of TV-45070-treated patients reported 30% or greater ( $p<0.05$ ) and 50% or greater ( $p<0.05$ ) reduction in their pain compared to placebo.

TV-45070 was studied in both a topical formulation and an oral formulation in small, exploratory Phase 2 proof-of-concept clinical trials in primary EM. EM is a disorder of severe neuropathic pain where, in certain families, mutations causing increased activity of the Nav1.7 sodium channel have been identified. The disorder is characterized by recurrent flares of intense burning pain with redness of the skin in the feet, hands or both. We conducted a randomized, double-blind, placebo-controlled, two-period crossover design trial with four subjects comparing oral TV-45070 to placebo each administered twice per day for a duration of two days. In one treatment period, subjects received TV-45070 (400 mg bid), and in the other treatment period, subjects received placebo. The order in which the subjects received each treatment was randomized. In this oral Phase 2 EM trial, a significant (42%) reduction in pain in the two hours following an induced EM flare was observed in the three patients where pain was induced ( $p=0.014$ ). There were no SAEs in this trial and the most frequently reported adverse events were dizziness, headache, sedation and drowsiness, which ranged from mild to severe.

We also conducted a randomized, double-blind, placebo-controlled design trial with eight subjects (seven TV-45070 and one placebo) comparing topical 8% TV-45070 to placebo applied two times per day to the feet for a duration of 14 or 21 days. Throughout the trial, TV-45070 plasma concentrations were low and TV-45070 was well-tolerated. There was no treatment-related dizziness and drowsiness and there were no treatment-related SAEs. Local application site reactions were the most common drug-related adverse events observed. In this topical Phase 2 EM trial, three of seven patients (43%) on TV-45070 showed consistent clinically meaningful reductions in induced and daily pain compared to baseline, while the four remaining TV-45070-treated and placebo-treated subjects were considered to be non-responders based on their magnitude of response or inconsistent response or both. Also, four of six (67%) patients on TV-45070 who used rescue cooling showed a reduction in cooling usage compared to baseline and six of seven (86%) patients on TV-45070 had an improvement in sleep interference scores compared to baseline. This small exploratory trial was not designed to reach statistical significance and no such statistical significance was found. Although we and Teva have evaluated the opportunity to develop TV-45070 as a treatment for EM, Teva is currently focused on the development of TV-45070 for larger market opportunities, such as PHN, and has no current development plans for TV-45070 in EM.

We conducted a Phase 2 proof-of-concept trial of topical TV-45070 in 70 PHN patients. Patients enrolled into the study had refractory PHN and their average disease duration was 76.6 months. This study was a double-blind, placebo-controlled, crossover trial where topical (8% ointment) TV-45070 was administered twice daily with each patient receiving either TV-45070 or placebo for three weeks, then after a washout period, the subjects received the alternative treatment. In this study, Topical TV-45070 was well-tolerated with no drug-related SAEs. The results showed there was a reduction in the primary efficacy endpoint (change from baseline in the mean daily pain score) for both TV-45070 and placebo, but the difference between treatments was not statistically significant. In analysis of certain secondary endpoints, there was a significantly increased proportion of TV-45070-treated patients who reported 30% or greater ( $p=0.049$ ) and 50% or greater ( $p=0.0078$ ) reduction in their pain compared to placebo and a retrospective exploratory analysis not described in the study protocol showed that a significant increased proportion of TV-45070-treated patients reported 30% or greater improvement in sleep ( $p=0.034$ ) compared to placebo. There is a

relatively common genetic variant of Nav1.7 called the R1150W gene variant. We genotyped a subset of the PHN trial subjects for R1150W status to explore if the variant could predict a greater likelihood of response to TV-45070 due to its inhibition of Nav1.7. Although it was not a pre-selected endpoint of the trial, a trend towards greater response to TV-45070 was observed in R1150W-carriers versus non-carriers, as five out of the eight evaluable subjects (63%) had a 30% or greater reduction in their pain when treated with TV-45070. TV-45070 plasma concentrations were low and TV-45070 was well-tolerated with no drug-related SAEs. No drug-related centrally mediated side effects of dizziness and drowsiness were observed in this study. In addition, while on topical TV-45070, PHN patients reported reduced site application pain (3% TV-45070 versus 16% placebo) and less pruritus, or itch, (3% TV-45070 versus 13% placebo) compared to while on placebo treatment. Chronic itch is an important co-morbidity for many PHN patients. The most frequently reported AEs included local application site reactions, nasopharyngitis and urinary tract infections.

#### TV-45070 Phase 2b Clinical Trial in OA

Using a topical (4% and 8% ointment) formulation of TV-45070, Teva completed a 300-patient, double-blind, placebo-controlled, randomized Phase 2b clinical trial designed to evaluate the safety and efficacy of topically applied TV-45070 in patients with chronic pain due to OA of the knee. In July 2015, we and Teva announced top line results showing that TV-45070 did not demonstrate statistically significant difference from placebo in efficacy endpoints of reductions in pain due to OA. However, TV-45070 did demonstrate a favorable safety and tolerability profile, with no drug-related SAEs. The most common adverse events were application site dermal skin reactions which were mostly mild and less frequent than seen with other topical analgesics. There were no cardiac or central nervous system safety issues. There are no plans for further development of TV-45070 in OA and future clinical development of TV-45070 is focused on neuropathic pain, including PHN.

#### TV-45070 Phase 2b Clinical Trial in PHN

Based on the encouraging data from our Phase 2 proof-of-concept trial in PHN, Teva is currently conducting a larger Phase 2b trial in patients with PHN. The rationale supporting the development of TV-45070 in PHN includes:

- We observed promising efficacy findings in our PHN Phase 2 proof of concept trial.
- We observed improved responder rates for carriers of the R1150W variant in our PHN Phase 2 proof of concept trial.
- Topical TV-45070 has exhibited an ability to penetrate the skin of PHN patients and reside locally, in both the skin and underlying tissue, at relatively high concentrations.
- Application of TV-45070 to the human torso in Phase 1 and Phase 2 clinical trials to date resulted in low systemic exposure of TV-45070, which may reduce systemic adverse events.
- Central nervous system, or CNS, side effects were not observed in the topical PHN trial due to low plasma levels, which we believe is a benefit given evidence that PHN patients have shown poor compliance with products that trigger common CNS side effects.
- Topical TV-45070 in the PHN Phase 2 proof-of-concept trial reduced the incidence of itch compared to placebo.
- Lidocaine, a weak sodium channel blocker, provides relief of PHN pain and is approved and widely used for this indication.

The Phase 2b trial is a randomized, double-blind, placebo controlled, multi-site study to evaluate the efficacy and safety of TV-45070 in patients with PHN. The study includes three treatment groups that receive doses of 4% or 8% of TV-45070 or placebo, dosed twice daily. Approximately 330 patients will be enrolled in the study. Patients will be stratified into treatment groups based on their R1150W status, a genetic pain biomarker believed to be related to pain susceptibility. The primary endpoint of this study is the change from baseline to week 4 in the numeric rating scale, or NRS, scores. Secondary endpoints include additional pain measurement scores at specified daily time points, the percentage of patients with greater than 30% and greater than 50% improvement in pain scores, quality of life measurements and adverse events measurements. The first patient was enrolled in April 2015, and results are expected in the second half of 2016.

#### About Post-Herpetic Neuralgia

PHN is a painful complication of Herpes zoster infection, occurring particularly in patients above the age of 50. Herpes zoster, otherwise known as shingles, generally manifests as a painful skin rash with blisters in a limited area on one side of the body. Pain can occur both before and during the rash, and can also persist after the infection has resolved. PHN is defined as pain that persists for 120 days or longer after the onset of rash. It is estimated that the annual incidence of Herpes zoster is between 230 and 630 cases per 100,000 people, with PHN occurring in approximately 20% of cases, resulting in approximately 200,000 PHN patients in the U.S.

Like other forms of neuropathic pain, there is a need for improved treatments for PHN. The current leading drugs used to treat PHN suffer from low efficacy for many patients and common dose limiting side effects. It has been reported that 30% to 50% of PHN patients achieve a 30% to 50% improvement in their pain with these agents. Currently prescribed treatments include Pfizer's Lyrica, and generic forms of gabapentin, both of which target the same mechanism. Common side effects for these drugs include sleepiness, dizziness, blurred vision, edema and weight gain.

GDC-0276, GDC-0310, and Other Selective Inhibitors of Nav1.7 for the Treatment of Pain

In December 2011, we entered into a collaborative research and license agreement with Genentech and its affiliate, F. Hoffman-La Roche Ltd, or Roche, to discover and develop selective oral inhibitors of Nav1.7 for the treatment of pain. For a more detailed description of the terms of this agreement with Genentech, see “—Strategic Alliances” below. Based on our discovery of Nav1.7 deficiency underlying CIP, we believe that Nav1.7 is a highly-validated target for the treatment of pain. Our Genentech collaboration is focused on discovering and developing selective oral Nav1.7 inhibitors, which is in contrast to our Teva partnership that is focused on developing a topical drug that targets a number of different sodium channels, including Nav1.7.

Genentech is currently conducting Phase 1 clinical trials for GDC-0276 and GDC-0310, which are both oral, selective Nav1.7 small-molecule inhibitors being developed for the potential treatment of pain. Both Phase 1 clinical trials are ongoing, and pending a full assessment of the results, Genentech intends to initiate a Phase 2 trial in 2016.

To study the effects of targeting Nav1.7 for the treatment of pain, we developed an animal model of inherited EM, or IEM, by expressing human Nav1.7 carrying a known IEM mutation in mice. These mice demonstrate a greater sensitivity to pain. As shown in the figure below, with a single dose of GDC-0276, these mice have fewer pain events demonstrating the ability of GDC-0276 to inhibit Nav1.7 in vivo.

Chronic pain conditions, such as severe cancer pain and neuropathic pain, are generally recognized as unmet medical needs providing potential commercial opportunities for a new oral pain drug. Currently available pain drugs often have either a lack of meaningful pain relief or dose limiting side effects for many patients. An orally administered selective Nav1.7 inhibitor could present a novel mechanism for the treatment of moderate to severe pain as a single agent or in combination with existing analgesics that work through different mechanisms. This mechanism contrasts with our non-selective sodium channel inhibition approach taken with TV-45070. We believe that the selective inhibition of Nav1.7 may lower the potential for dose-limiting central nervous system side-effects and allow for an improved side-effect profile for oral administration of such an inhibitor, which could potentially allow for the treatment of pain that has a central or deep tissue component, including cancer pain and neuropathic pain.

We formed a second collaboration with Genentech in March 2014 for pain genetics, where we intend to focus on rare phenotypes where individuals have an inability to perceive pain or where individuals have non-precipitated spontaneous severe pain. For a more detailed description of the terms of this second agreement with Genentech, see “—Strategic Alliances” below. We believe these phenotypes may unlock new key molecular regulators of pain signaling in humans, which we will seek to validate as targets for new pain drugs. For example, we are analyzing CIP families that are not explained by Nav1.7 deficiency as well as families with conditions associated with severe pain phenotypes such as paroxysmal extreme pain disorder, or PEPD, inherited EM and cluster headache.

## Selective Small-Molecule Inhibitors of Targets for the Treatment of Cardiovascular Disease

We entered into a collaborative research and option agreement with Merck in June 2009 to discover novel targets and compounds for the treatment of cardiovascular disease using our Extreme Genetics discovery platform. For a more detailed description of the terms of our agreement with Merck, see “—Strategic Alliances” below. In 2012, Merck exercised its option to obtain an exclusive license to a target for cardiovascular disease and compound inhibitors that were discovered during the research collaboration. The target, when inhibited, is predicted to provide a beneficial lipid profile with the goal of protecting from cardiovascular disease.

## Our Proprietary Product Candidates

### XEN801 for the Treatment of Acne

XEN801 is a selective, small molecule inhibitor of SCD1 being developed for the treatment of moderate to severe acne. SCD1 is an enzyme involved in lipid synthesis that is expressed in sebaceous glands in the skin. Mice deficient in SCD1 have a marked phenotype of sebaceous gland atrophy suggesting that inhibition of SCD1 activity in the skin may provide a novel treatment option for disorders of enlarged or overactive sebaceous glands, including acne. Published literature studying animals deficient in skin SCD1 have shown that these animals have lower levels of certain lipids produced by sebaceous glands, increased levels of retinoic acid, and increased levels of retinoic acid induced proteins including greatly elevated expression of Lipocalin-2, or LCN2, a gene which transcribes neutrophil gelatinase-associated lipocalin, or NGAL. NGAL has been shown to mediate sebaceous gland cell death and may also have antibacterial properties. LCN2 is also highly upregulated and NGAL levels increased in a human sebaceous gland cell line treated with a SCD1 inhibitor. Published reports on isotretinoin, an approved acne treatment, also support the theory that isotretinoin’s therapeutic effects are achieved in part through increasing levels of NGAL.

We have discovered and developed novel small-molecule SCD1 inhibitors to which we have sole rights. In multiple animal models, we have shown that our SCD1 inhibitors can reduce the size and number of sebaceous glands. XEN801 has demonstrated good properties for topical administration including formulation in a light gel and adequate skin penetration in multiple animal species.

In preclinical mouse models, XEN801 applied topically showed reduction in the size of sebaceous glands in the underlying skin in a time and dose dependent manner.

In these preclinical mouse efficacy studies, at the vehicle treated sites, numerous normally sized lipid loaded sebaceous glands are visible whereas only very small sebaceous glands with hardly any visible lipids are present at the XEN801 treated sites. These reductions are visible after two days of twice-daily treatment and reached statistical significance after seven days (data presented in the above figure), reverting to normal levels once the treatment is stopped. Skin areas distant from the XEN801 treated sites exhibit no changes in sebaceous glands which is consistent with the observed low plasma concentrations of XEN801 and the high local concentrations found in the skin at the treated sites.

We believe these properties support the local treatment of acne and other dermatological disorders with topical XEN801 by decreasing the size of the sebaceous glands, while leaving the skin in other areas unaffected and not exposed unnecessarily to high drug concentrations.



## Clinical Development of XEN801

In September 2015, we initiated a Phase 1 clinical trial of XEN801, which was completed by the end of the year. In the Phase 1 study, XEN801 was found to be safe and generally well tolerated. In total, 48 healthy volunteers were dosed for either a 14-day or 21-day treatment period. A number of different dose volumes of the 1% XEN801 drug product were evaluated in the Phase 1 clinical trial with dosing on the back and face of healthy volunteers to determine the maximum tolerated dose. As expected, the most common side effects were localized, generally mild skin reactions. No serious adverse events were observed. Maximal plasma concentrations of XEN801 were low, whereas the median skin concentration of XEN801 was above the drug concentration predicted for efficacy for all dose volumes evaluated. A Phase 2 dose was selected based on favorable tolerability and skin drug concentrations.

In February 2016, we initiated a Phase 2 clinical trial in patients with moderate to severe acne. The Phase 2 clinical trial is a randomized, double-blind, multi-center, vehicle-controlled, parallel-group study to determine the safety, tolerability, efficacy and systemic exposure of XEN801 in approximately 150 patients with moderate to severe facial acne. Patients will apply XEN801 (or vehicle placebo) topically to their face for 12-weeks with a 4-week follow up. The primary efficacy endpoint is the percent change in total (inflammatory and non-inflammatory) lesion count from baseline to week 12. Secondary endpoints include the percent change in inflammatory and/or non-inflammatory lesions at different time points throughout the 12 week study as well as a number of Investigator's Global Assessment measures. We anticipate topline results in the fourth quarter of 2016.

## About Acne

Acne is a multifactorial disease of the pilosebaceous unit, which are skin structures consisting of a hair follicle and its associated sebaceous gland. Increased levels of androgens, such as testosterone, which occurs during puberty cause an enlargement of the sebaceous gland that increases the amount of sebum, a naturally occurring oil, production. Acne develops as a result of blockages in the hair follicles due to the sebaceous glands becoming clogged with excess sebum and dead skin cells. Under these conditions, the bacteria *Propionibacterium acnes* can multiply and cause the noticeable inflammatory lesions. We believe that topically applied SCD1 inhibitors will treat acne at its root cause by reducing the underlying sebaceous gland enlargement and reducing sebum production. With its association with the onset of puberty, acne prevalence peaks in late adolescence and is estimated to affect 40 to 50 million people in the U.S, of which there are approximately 11 million and 1.2 million individuals with moderate and severe acne, respectively.

Milder forms of acne are normally treated with over the counter products such as those containing benzoyl peroxide whereas moderate and severe forms of acne are often treated with the prescription drug isotretinoin. Isotretinoin is effective with the majority of patients reporting an improvement and approximately 50% of patients reporting remission of their acne. Scientific studies have shown that isotretinoin can cause apoptosis, a form of cell death, in sebaceous glands thereby reducing sebum production. Isotretinoin treatment has been associated with relatively common side effects including thin and dry skin, hair loss, severe acne flares, blood lipid and liver enzyme elevations. However, the most significant adverse event of isotretinoin is birth defects if taken by women during pregnancy or even a short time before conception due to its teratogenic potential. In 2005, the FDA approved a risk management plan for isotretinoin called iPLEDGE. Under this program, general practitioners are prohibited to prescribe isotretinoin and patients are referred to dermatologists registered and activated in the iPLEDGE program. In addition, patients are also required to register and qualify for the iPLEDGE program. Isotretinoin can only be dispensed for a 30-day supply (no refills) by a registered pharmacy. We believe that a safer alternative drug (without an onerous risk mitigation plan) that potentially reduces sebum production may be a significant treatment option for moderate to severe acne.

## Selective Small-Molecule Sodium Channel Inhibitors for the Treatment of Severe Childhood Epilepsy Disorders



We are developing selective inhibitors of the voltage-gated sodium channel Nav1.6 as a treatment for severe childhood epilepsy disorders, such as the orphan disease DS. We have developed considerable expertise in voltage-gated sodium channel biology and have accumulated significant experience in the development of selective sodium channel inhibitors. We are leveraging this expertise and chemistry know-how for the development of selective inhibitors of Nav1.6 for the treatment of severe childhood epilepsy disorders, such as DS.

With our collaborators from McGill University, we identified the genetic link between rare human epilepsy and mutations in the Nav1.1 gene. For example, it is now estimated that approximately 80% of DS cases are believed to be due to mutations in one copy of the Nav1.1 voltage-gated sodium channel that cause a partial loss of Nav1.1 function. Nav1.1 plays a critical role in the normal functioning of inhibitory pathways in the brain. The lack of fully functioning Nav1.1 and inhibitory pathways allows the brain excitatory pathways to be unopposed resulting in the severe seizures of DS. The brain excitatory pathways are preferentially mediated by the voltage-gated sodium channel Nav1.6 and therefore if we are able to selectively inhibit Nav1.6 with a small-molecule compound, we expect to taper this neuronal excitation and thereby treat rare forms of severe childhood epilepsy, such as DS. To further support inhibiting Nav1.6 as a potential therapeutic approach to treat DS and other forms of rare epilepsy, published data has shown that seizures and premature death observed in a DS mouse model can be corrected when these animals are bred with a Nav1.6 knockout mouse. While DS is one of the most resistant epilepsies to treatment, there are other intractable childhood seizures that have been associated with genetically-linked partial loss of function of Nav1.1 or gain of function of Nav1.6, which may benefit from a selective inhibitor of Nav1.6, including intractable childhood epilepsy with generalized tonic-clonic seizures and sporadic infantile epileptic encephalopathy.

Based on our experience and know-how in developing selective ion channel inhibitors, we have identified potent, selective Nav1.6 inhibitors and have demonstrated efficacy for seizures in an animal model with such an inhibitor. We expect to identify a development candidate in 2016 and file an IND application in the first half of 2017. Given the orphan nature of severe childhood epilepsies, including DS, we believe that these indications may represent attractive opportunities for us to independently develop and commercialize product candidates.

#### New Pipeline Opportunities

In addition to our study of rare human disorders of extreme pain or the absence of pain, we are also studying other rare disorders with extreme phenotypes that we believe could yield new drug targets in disorders where high medical need exists. Given our expertise in ion channel drug discovery, we are also focusing our discovery efforts on the identification of ion channel targets where we believe novel selective inhibitors might represent significant therapeutic advances with a focus on orphan indications.

#### Strategic Alliances

##### Agreement with uniQure for Glybera

Effective August 2000, we entered into a sublicense and research agreement with uniQure (formerly Amsterdam Molecular Therapeutics) pursuant to which we granted to uniQure an exclusive, worldwide sublicense under certain intellectual property controlled by us to develop and commercialize technology and compounds related to the variant of LPL, called LPL<sup>S447X</sup>. Together with collaborators from UBC, we demonstrated that the LPL<sup>S447X</sup> variant resulted in increased LPL enzyme activity leading to reduced triglyceride levels in humans. Under our sublicense and research agreement with uniQure, we collaborated with uniQure and UBC on preclinical activities, and thereafter uniQure developed an LPL gene therapy product, Glybera, which contains the LPL<sup>S447X</sup> variant. Glybera was approved in the EU in October 2012 to treat LPLD in patients with severe or multiple pancreatic attacks despite dietary fat restrictions. uniQure conducted the clinical trials and is responsible for the commercialization of Glybera.

Under the terms of the agreement, we are eligible to receive mid single-digit royalties on net sales of the licensed products, for sales made by uniQure and its affiliates. The royalty rates are reduced to a low single-digit for sales made by uniQure and its affiliates in countries where a licensed technology or a licensed product is not covered by a valid patent claim. Such royalties are payable until the expiration of the last licensed patent from UBC. With respect to uniQure's sublicense to Chiesi, we are eligible to receive a percentage in the low twenties of all non-royalty compensation relating to the licensed technology or products that uniQure receives from Chiesi (for example upfront

payments and milestone payments), a percentage in the low twenties of any royalties that uniQure receives from Chiesi based on sales of technology or products covered by the licensed patents, plus a mid single-digit percentage of certain further royalties that uniQure receives from Chiesi based on sales of our licensed technology or products after the expiration of all licensed patents covering the licensed technology or products during the period expiring ten years after the date of the first sale by or on behalf of Chiesi. If uniQure grants a sublicense to a third party other than to Chiesi, then we are eligible to receive a percentage in the low twenties of all non-royalty compensation relating to the licensed technology or products that uniQure receives from such sublicensee (for example upfront payments and milestone payments), plus a percentage in the low twenties of any royalties that uniQure receives from such sublicensee based on sales of technology or products covered by the licensed patents. Although commercial sales of Glybera commenced in the fourth quarter of 2015, we do not expect to receive significant revenue in the near-term from these sales. Furthermore, royalties we are eligible to receive pursuant to our agreement with uniQure, including royalties related to sales made by Chiesi, are subject to customary royalty stacking deductions in the event that uniQure, or any of its sublicensees, have to license other technologies in order to commercialize Glybera.

We are eligible to receive certain additional milestone payments of less than CAD\$1.0 million for Glybera and for each subsequent product, if any, developed pursuant to the agreement with uniQure. We, in turn, have certain payment obligations to our licensor, UBC, based on amounts received from uniQure or otherwise based on the exploitation of the licensed intellectual property.

Our sublicense agreement with uniQure expires on the date of the expiration of the UBC license agreement. Either party may terminate the agreement in the event of the other party's default under the agreement that remains uncured for 20 days after receipt of notice from the non-breaching party.

#### Agreement with UBC

Effective August 2000, we entered into a license agreement with UBC pursuant to which UBC granted to us an exclusive, worldwide license under UBC's interest in certain intellectual property controlled by UBC to develop and commercialize technology and compounds in the field of gene therapy, including products that related to the variant of LPL, called LPL<sup>S447X</sup>.

Under the terms of the agreement, UBC is eligible to receive certain pre-commercial milestone payments. UBC is also eligible to receive a mid single-digit percentage of certain compensation that we receive based on sublicenses granted by us to a third party relating to the licensed technology or products, including in connection with our sublicensing agreement with uniQure for LPL<sup>S447X</sup>.

Through December 31, 2015, we have paid to UBC upfront fees and milestone payments totaling CAD\$271,000 and are obligated to pay a certain additional milestone payment of approximately CAD\$200,000 for Glybera and further milestone payments of CAD\$322,500 for each subsequent product, if any, developed pursuant to our sublicensing agreement with uniQure.

Our license agreement with UBC expires on the date of the expiration of the last patent granted under such license. In the event that our sublicense with uniQure is terminated, we may terminate the agreement with 30 days advance notice to UBC. Either party may terminate the agreement in the event of the other party's default under the agreement that remains uncured for 30 days after receipt of notice from the non-breaching party, and UBC may terminate without such cure period in the event of certain types of breach by us.

#### Agreement with Teva for TV-45070

In December 2012, we entered into a collaborative development and license agreement with Teva, through its subsidiary, Ivax, pursuant to which we granted Teva an exclusive worldwide license to develop and commercialize certain products, including TV-45070. Under the terms of the agreement, Teva paid us an upfront fee of \$41.0 million. We are collaborating with Teva to further develop TV-45070, and Teva is funding all development costs with respect to the licensed products. In addition, we are eligible to receive potential milestone payments totaling up to \$335.0 million, comprised of a \$20.0 million clinical milestone payment, up to \$285.0 million in regulatory milestone payments, and a \$30.0 million sales-based milestone payment. If TV-45070 is approved, we are also eligible to receive royalties in the low teens to the low twenties on net sales of the licensed products for the timeframe ending upon the latest of (a) expiration of the last valid claim of a licensed patent covering the product, (b) the date on which such product loses market exclusivity and (c) the 10th anniversary of first commercial sale, in each case on a country-by-country basis.

We have an option to a 20% to 30% co-promotion interest for products incorporating TV-45070 in the U.S. Our exercise of this option is subject to meeting objective financial conditions, staffing requirements and compliance standards to be determined in Teva's reasonable discretion in accordance with standard industry practice. Our

co-promotion option is exercisable upon the filing of the first new drug application, or NDA, for a TV-45070 product with the FDA and we will be obligated to pay an opt-in fee to Teva, which is calculated by multiplying our co-promotion interest (as a percentage) by the amount of certain milestones paid or payable by Teva, to which is added certain past and future development costs incurred by Teva with respect to the product for the U.S. Our co-promotion interest is in the 20% to 30% range, and equals our percentage share of detailing activities and co-promotion expenses. Such opt-in fee is payable as a reduction to the milestone payments or our share of operating profits that Teva would otherwise owe to us or a combination of the two. If we exercise this option, upon paying an opt-in fee to Teva, we will be eligible to receive, in lieu of royalties with respect to such product sales in the U.S., a percentage share (equal to our co-promotion interest) of operating profits from such product sales in the U.S.

Our agreement with Teva expires on the date of the expiration of all payment obligations to us under the agreement. Teva may terminate the agreement with 60 days advanced written notice to us after at least three Phase 2 (or later stage) clinical trials have been completed or in the event that safety or efficacy issues arise in the development of the licensed products. Either party may terminate the agreement in the event of the other party's material breach which remains uncured for 90 business days. In certain termination circumstances, we would receive licenses to Teva intellectual property relating to TV-45070 clinical development and regulatory filings. If patents within such Teva intellectual property cover the TV-45070 product, then Teva is eligible to receive royalties from us based on a percentage of net product sales, within the mid single-digit range. Pursuant to the terms of our agreement with Teva, an affiliate of Teva purchased 1,111,111 common shares in our initial public offering, based upon the initial public offering price of \$9.00 per share.

#### Agreements with Genentech for GDC-0276, GDC-0310, and Selective Inhibitors of Nav1.7 and Pain Genetics

In December 2011, we entered into a collaborative research and license agreement with Genentech and its affiliate, Roche, to discover and develop small and large molecules that selectively inhibit the Nav1.7 sodium channel and companion diagnostics for the potential treatment of pain. Pursuant to this agreement, we granted Genentech a worldwide exclusive license to develop and commercialize compounds directed to Nav1.7 and products incorporating such compounds for all uses. We also granted Genentech a worldwide non-exclusive license to diagnostic products for the purpose of developing or commercializing such compounds.

Under the terms of the agreement, Genentech paid us an upfront fee of \$10.0 million, a \$5.0 million milestone payment for the selection of GDC-0276 for development and an \$8.0 million milestone payment upon the approval by Health Canada of the clinical trial application, or CTA, for GDC-0276. Genentech is providing funding to us for certain of our full-time equivalents, or FTEs, performing the research collaboration plan. In addition, we are eligible to receive pre-commercial and commercial milestone payments with respect to the licensed products totaling up to an additional \$613.0 million, comprised of up to \$45.5 million in preclinical and clinical milestone payments, up to \$387.5 million in regulatory milestone payments, and up to \$180.0 million in sales-based milestone payments for multiple products and indications. In addition, we are eligible to receive royalties based on net sales of the licensed products, which range from a mid single-digit percentage to ten percent for small-molecule inhibitors for the timeframe that such products are covered by the licensed patents and a low single-digit percentage thereafter until the date that is ten years after first commercial sale on a country-by-country basis, plus a low single-digit percentage for large molecule inhibitors of Nav1.7 for a period of ten years from first commercial sale on a country-by-country basis.

Our agreement with Genentech expires on the date of the expiration of all payment obligations to us under the agreement. Genentech may terminate the agreement with three months advance notice anytime on or after the third anniversary of the effective date of the agreement, and each party may terminate the agreement in the event of a material breach by the other party that remains uncured after 90 days. In the event that Genentech terminates the agreement due to our breach, Genentech retains its licenses and its payment obligations to us are reduced. In the event that we terminate the agreement due to Genentech's breach, the rights and licenses granted to Genentech revert back to us, subject to certain rights to make and use certain large-molecule product candidates that are retained by Genentech, and Genentech is obligated to assign certain regulatory approvals and grant certain licenses to us to enable us to develop and commercialize certain terminated products outside of the collaboration.

In May 2015, we amended the collaborative research and license agreement to leverage the work performed in our ongoing Nav1.7 pain collaboration with Genentech for use in our research and development program directed towards modulators of Nav1.6 for use in the field of treating epilepsy, including DS. Pursuant to the amendment, we obtained a worldwide, non-exclusive, revocable license under intellectual property previously licensed by us to Genentech and intellectual property developed under the Nav1.7 collaboration that is necessary or useful to make and use certain Nav1.6 modulators for use in the field, excluding commercialization. We obtained a right of first negotiation for a

certain period of time to obtain a worldwide, exclusive license under the intellectual property licensed to us to commercialize certain Nav1.6 modulators to treat any disease in the field. We also granted Genentech a right of first negotiation to enter into a drug research and development collaboration with us for our Nav1.6 program. Genentech can terminate the license upon 90 days' notice after the third anniversary of the amendment or at any time upon our uncured material breach.

Pursuant to the amendment, we granted Genentech a worldwide exclusive license under intellectual property developed under our Nav1.6 program. The license permits Genentech to develop and commercialize compounds identified or first made in our Nav1.6 program for all uses outside the field of epilepsy and to develop and commercialize compounds (other than certain compounds identified or first made in our Nav1.6 program) for all uses. If Genentech reaches certain development milestones for and/or sells certain compounds identified or first made in our Nav1.6 program that are covered by a patent licensed to Genentech under the amendment, products containing such compound would be included in the products subject to the royalty and milestone obligations payable to us under the original agreement. The collaborative research and license agreement was amended again in December 2015 to extend the term of the research program.

In March 2014, we entered into an additional agreement with Genentech for pain genetics, where we intend to use our Extreme Genetics discovery platform to focus on identifying genetic targets associated with rare phenotypes where individuals have an inability to perceive pain or where individuals have non-precipitated spontaneous severe pain. Pursuant to the terms of this agreement, any intellectual property arising out of the collaboration will be jointly owned by us and Genentech. We have also granted Genentech a time-limited, exclusive right of first negotiation on a target-by-target basis to form joint drug discovery collaborations. Under the terms of this agreement, Genentech paid us an upfront payment of \$1.5 million, a \$0.25 million milestone payment related to the identification of a novel pain target in September 2015, and we are eligible for an additional \$1.75 million in milestone payments. The agreement terminates upon the expiration of Genentech's time-limited, exclusive right of first negotiation which shall be exercisable for two years. Genentech may terminate the agreement with three months advance notice anytime on or after the 12 month anniversary of the effective date of the agreement, and each party may terminate the agreement in the event of a material breach by the other party that remains uncured for 90 days. Furthermore, pursuant to the terms of a common share put agreement, an affiliate of Genentech, Roche Finance Ltd., invested approximately \$4.5 million in a private placement concurrent with our initial public offering at the same price per share as the initial public offering.

#### Agreement with Merck for Cardiovascular Disease

In June 2009, we entered into an exclusive collaborative research and option agreement with Merck, pursuant to which the parties conducted a research program to discover and develop novel small-molecule candidates for the potential treatment of cardiovascular disease. Merck provided payments to us for our FTEs who performed our activities pursuant to the research program conducted under the Merck agreement. The Merck collaborative research program ended in December 2012.

Under the terms of the agreement, Merck had the option to obtain an exclusive license under certain intellectual property controlled by us to develop and commercialize compounds and products directed to targets in the research program, which has now expired. In June 2012, Merck exercised its option and paid us \$2.0 million to obtain such a worldwide exclusive license to develop and commercialize compound inhibitors of a target that was identified using our Extreme Genetics discovery platform. Through December 31, 2015, we have received milestone payments and an option fee totaling \$9.0 million, and we are eligible for further research, development and regulatory milestone payments of up to \$64.0 million, comprised of \$21.0 million in preclinical and clinical milestone payments and up to \$43.0 million in regulatory milestone payments for products directed to the licensed target, as well as royalties from the mid to high single-digit range in countries where such products are covered by a valid composition or method of use claim of a Xenon or Merck patent or, if not covered by such claims, royalties in the mid single-digit range for ten years after first commercial sale of such products.

We have an option to co-fund the Phase 1 and first Phase 2 clinical trials of product candidates licensed by Merck by paying Merck 50% of such development costs. Such co-funding option is available at the IND-filing stage for the applicable product candidate. If we exercise our co-funding option then the maximum eligible milestone amounts due to us increase to \$86.5 million and the royalties increase to the high single-digit to the sub-teen double-digit range.

Our agreement with Merck expires on the date of the expiration of all royalty payment obligations to us under the agreement. Merck has the right to terminate the agreement upon providing certain notices to us. Each party may terminate the agreement in the event of a material breach by the other party that remains uncured for 90 days after notice of such breach. In the event that Merck terminates the agreement due to our breach, the licenses granted to Merck survive and becomes fully paid up. In the event that we terminate the agreement due to Merck's breach, the licenses granted to Merck terminate.

#### Intellectual Property



As part of our business strategy, we generally file patent applications disclosing and claiming the drug targets and their novel uses that we identified with the use of our Extreme Genetics discovery platform, novel compositions that modulate such targets, methods of making and using such compositions and various therapeutic formulations of such compositions that cover our product candidates. In some cases, we also file claims on screening assays as well as compositions and methods for use in diagnosing certain diseases. We generally file applications in the U.S., Canada, the EU and other commercially significant foreign jurisdictions. We also rely on trade secrets, internal know-how, technological innovations and agreements with third parties to develop, maintain and protect our competitive position. Our ability to be competitive will depend on the success of this strategy.

As of December 31, 2015, we owned, co-owned or licensed 56 issued or allowed U.S. patents and approximately 20 pending U.S. patent applications, including provisional and non-provisional filings. We also owned, co-owned or licensed an additional 639 pending and granted counterpart applications worldwide, including 161 country-specific validations of 11 European patents.

We have in-licensed from UBC patent applications and patents related to Glybera, and methods of making and using Glybera. These include European Patent No. 1,200,117, Japanese Patent No. 5,095,894, Canadian Patent No. 2,370,081 and the allowed U.S. Patent Application No. 14/324,151. European Patent No. 1,200,117, Japanese Patent No. 5,095,894 and Canadian Patent No. 2,370,081, are expected to expire in June 2020 (absent any extensions of term); U.S. Patent Application No. 14/324,151, when issued, is expected to expire in June 2020 (absent any extensions of term). In addition, U.S. Patent No. 6,814,962 has claims directed to the use of various recombinant viruses containing LPL coding sequences to treat various pathologies and is expected to expire in November 2020 (absent any extensions of term).

As of December 31, 2015, we owned eight issued U.S. patents and seven pending U.S. patent applications related to TV-45070, and methods of making and using this and certain related compounds. The issued patents are expected to expire between 2026 and 2030 (absent any extensions of term). In addition, we have 67 foreign issued patents (exclusive of European patent national validation) and have filed 145 corresponding applications in various foreign jurisdictions relating to TV-45070 and certain related compounds.

As of December 31, 2015, we, together with Genentech, co-owned two issued U.S. patents, two pending U.S. patent applications and 30 pending counterpart patent applications worldwide relating to GDC-0276 and methods of making and using this and certain related compounds. The issued patents, as well as patents issuing from these applications are expected to expire in 2033 (absent any extensions of term). We also co-owned with Genentech one pending U.S. patent application, one pending PCT international application, and three corresponding applications in various foreign jurisdictions relating to GDC-0310 and certain related compounds. Any patents issuing from these applications are expected to expire between 2034 and 2035 (absent any extensions of term).

As of December 31, 2015, we owned or co-owned four issued U.S. patents related to XEN801, and methods of making and using this and certain related compounds. These issued patents are expected to expire between 2024 and 2028 (absent any extensions of term). In addition, we have 27 foreign issued patents (exclusive of European patent national validation) and have filed nine corresponding applications in various foreign jurisdictions relating to XEN801 and certain related compounds.

We may obtain patents on our novel compositions before we obtain marketing approval for product candidates containing such compositions. Because patents are only valid for a limited period, and the life of a particular patent may begin prior to the commercial sale of the related product, the commercial value of any patent is limited. However, in certain circumstances, we may be able to seek patent term extensions for patents in the U.S. and in a number of European countries, compensating in part for delays in obtaining marketing approval, but we cannot be certain we will obtain such extensions.

Further, the existence of issued patents does not guarantee our right to practice the patented technology or commercialize any product candidate covered by such a patent. Third parties may have or obtain rights to other patents that could be used to prevent or attempt to prevent us from commercializing our product candidates. If these other parties are successful in obtaining valid and enforceable patents, and establishing our infringement of those patents, we could be prevented from commercializing our product candidates unless we were able to obtain a license under such patents, which may not be available on commercially reasonable terms or at all.

In the conduct of our business, we may infringe patents or other proprietary rights of third parties. If we do infringe such patents or other proprietary rights, we could be prevented from developing or selling products or from using the processes covered by those patents, could be required to pay substantial damages or could be required to obtain a license from the third party to allow us to use their technology, which may not be available on commercially reasonable terms or at all. If we are not able to obtain a required license or develop alternative technologies, we may be unable to develop or commercialize some or all of our products, and our business could be adversely affected.

Much of our scientific capabilities depend upon the knowledge, experience and skills of key scientific and technical personnel. To protect our rights to our proprietary know-how and technology, we require all our employees, consultants and advisors to enter into confidentiality agreements that require disclosure and assignment to us of ideas, developments, discoveries and inventions made by these employees, consultants and advisors in the course of their service to us.

We may be unable to obtain, maintain and protect the intellectual property rights necessary to conduct our business, and we may be subject to claims that we infringe or otherwise violate the intellectual property rights of others, which could materially harm our business. Although we believe our patents and patent applications provide us with a competitive advantage, the patent positions of biotechnology and pharmaceutical companies can be uncertain and involve complex legal and factual questions. We and our collaborators may not be able to develop patentable product candidates or processes or obtain patents from pending patent applications. Even if patent claims are allowed, the claims may not issue, or in the event of issuance, may not be sufficient to protect the technology owned by or licensed to us or to our collaborators. In certain cases where we have licensed rights to our intellectual property to our collaborators, such collaborators have assumed control of the prosecution and maintenance of the intellectual property portfolio related to such licensed rights. If our collaborators fail to adequately prosecute or maintain any portion of our licensed intellectual property, the competitive advantage and value of our intellectual property portfolio may be reduced. For more information, see “Risk Factors—Risks Related to Our Intellectual Property Rights.”

We own a number of trademarks and intend to develop names for our product candidates and as appropriate seek to secure trademark protection for them, including domain name registration, in relevant jurisdictions.

### Competition

The biotechnology and pharmaceutical industries are highly competitive and are characterized by rapidly advancing technologies and a strong emphasis on proprietary products. While we believe that our technology, development experience, scientific knowledge and drug discovery approach provide us with certain advantages, we face potential competition in target discovery and product development from many different approaches and sources, including pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates or products that we or our collaborators successfully develop and commercialize will compete with existing products and new products that may become available in the future.

With respect to target discovery activities, competitors and other third parties, including academic and clinical researchers, may be able to access rare families and identify targets before we do.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaboration arrangements with large and established companies.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of alternative products, the level of competition and the availability of coverage, and adequate reimbursement from government and other third party payers.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products or therapies that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA, European Medicines Agency, or EMA, or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third party payers seeking to encourage the use of generic products.

Aside from the product marketplace, our competitors also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites, recruiting patients for clinical trials, and by acquiring technologies complementary to, or necessary for, our programs.

Our partnered products and proprietary product candidates that are currently approved or are in clinical development may compete with various therapies and drugs, both in the marketplace and currently under development.

#### Glybera (alipogene tiparvovec) Competition

There are no approved gene therapies currently on the market for LPLD. The current management of LPLD consists of strict adherence to an extremely low-fat diet, but compliance with such a diet is challenging. Lipid-lowering drugs are generally not effective for treating LPLD. We are not aware of any other drugs or therapies currently in development that treat LPLD by using the LPL sequence containing the LPL<sup>S447X</sup> genetic variant or otherwise.

#### TV-45070, GDC-0276, and GDC-0310 Competition

Drug discovery and development for various pain applications is intensely competitive. There are a large number of approved products for neuropathic pain, inflammatory pain and other pain indications. These approved products include capsaicin, celecoxib, lidocaine, narcotic analgesics and pregabalin. We are also aware of clinical-stage development programs at several pharmaceutical and biotechnology companies that are developing Nav1.7 inhibitors or other sodium channel inhibitors for the treatment of pain, including Biogen Inc., Dainippon Sumitomo Co., Ltd., Eli Lilly and Company, Merck, NeuroQuest Inc., and Vertex Pharmaceuticals Inc. Moreover, we are aware of various other product candidates in development that target other mechanisms of action to treat various pain indications, including calcium channel inhibitors, nerve growth factor inhibitors and P2X purinoceptor 3 inhibitors.

#### XEN801 Competition

If XEN801 were approved for the treatment of acne, we anticipate it would compete with other approved prescription acne products including topical retinoids, oral hormonal therapies, topical and oral antimicrobials, and oral isotretinoin. In addition to approved prescription therapies, there are a wide range of over-the-counter, or OTC, treatments targeted at treating acne. Additionally, there are a number of prescription products that are used “off-label” for the treatment of acne. We are also aware of several products in clinical development that could potentially compete with XEN801, including products in development from Allergan PLC, AOBiome LLC, Braintree Laboratories Inc., Cassiopea SpA, Dermira Inc., Foamix Pharmaceuticals Ltd., Galderma SA, Mimetica Pty Ltd, Novan Therapeutics, Phosphagenics Ltd, Valeant Pharmaceuticals, and XBiotech Inc.

#### Government Regulation

We are developing both small-molecule and large-molecule product candidates. Our small-molecule product candidates are regulated as drugs by the FDA. The gene therapy product, Glybera, would be regulated by the FDA as a biologic. Within the FDA, the Center for Drug Evaluation and Research, or CDER, regulates drugs and the Center for Biologics Evaluation and Research, or CBER, regulates biological products. Drugs and biological products are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and other federal, provincial, state, local and foreign statutes and regulations. Biological products are also subject to regulation under the Public Health Service Act, or PHS Act. Both the FD&C Act and the PHS Act, as applicable, and their corresponding regulations govern, among other things, the testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, import, export, reporting, advertising and other promotional practices involving drugs and biological products. FDA approval must be obtained before clinical testing of drugs or biological products is initiated, and each clinical study protocol for such product candidates is reviewed by the FDA prior to initiation in the U.S. FDA approval also must be obtained before marketing of drugs and biological products in the U.S. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, provincial, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Federal and state agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. In particular, ethical, social and legal concerns about genetic testing, genetic research and gene therapy could result in additional regulations restricting or prohibiting the processes we may use in discovering and developing our products candidates and in manufacturing and marketing Glybera and any other gene therapy products we or our collaborators may develop. More restrictive regulations or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

## U.S. Drug Development Process

The process required by the FDA before a drug or biological product may be marketed in the U.S. generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to good laboratory practices, or GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical studies may begin;
- performance of adequate and well-controlled human clinical studies according to the FDA's regulations commonly referred to as good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed product for its intended use;

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- submission to the FDA of an NDA for drug products or a biological license application, or BLA, for biological products for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical studies;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the product is produced to assess compliance with good manufacturing practices, or GMP, to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the NDA or BLA; and
- FDA review and approval of the NDA, or licensure of the BLA.

Before testing any drug or biological product candidate in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

The clinical study sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical study on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical study can begin. The FDA may also impose clinical holds on a product candidate at any time before or during clinical studies due to safety concerns or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical studies to begin, or that, once begun, issues will not arise that suspend or terminate such studies.

Clinical studies involve the administration of the drug or biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical studies are conducted under protocols detailing, among other things, the objectives of the clinical study, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical study will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical studies must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical study must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical study will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical studies are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical study subject or his or her legal representative and must monitor the clinical study until completed.

Human clinical studies are typically conducted in three sequential phases that may overlap or be combined:

- Phase 1. The drug or biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- Phase 2. The drug or biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.



Phase 3. Clinical studies are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical study sites. These clinical studies are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for product labeling.

Post-approval clinical studies, sometimes referred to as Phase 4 clinical studies, may be conducted after initial marketing approval. These clinical studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects in studies of gene therapy products for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects. During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical study investigators.

Concurrent with clinical studies, companies usually complete additional animal studies and must also develop additional information about the physical characteristics of the drug or biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with GMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final drug or biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug or biological product candidate does not undergo unacceptable deterioration over its shelf life.

Human gene therapy products are a new category of therapeutics, and studies of gene therapy products are subject to certain regulatory requirements in addition to those set forth above including certain requirements of the National Institutes of Health.

#### U.S. Review and Approval Processes

After the completion of clinical studies of a drug or biological product, FDA approval of an NDA or a BLA must be obtained before commercial marketing of the drug or biological product, respectively. The NDA or BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. In addition, under the Pediatric Research Equity Act, or PREA, an NDA or a BLA or supplement to an NDA or a BLA must contain data to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug or biological product for an indication for which orphan designation has been granted. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the NDA or BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA or BLA must be accompanied by a substantial user fee. PDUFA also imposes an annual product fee for drugs and biologics and an annual establishment fee on facilities used to manufacture prescription drugs or biologics. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs or BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

Within 60 days following submission of the application, the FDA reviews an NDA or BLA submitted to determine if it is substantially complete before the agency accepts it for filing. The FDA may refuse to file any marketing application that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the NDA or BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the NDA or BLA. The FDA reviews the application to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with GMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel products or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory

committee, but it considers such recommendations carefully when making decisions. During the product approval process, the FDA also will determine whether a Risk Evaluation and Mitigation Strategy, or REMS, is necessary to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the NDA or BLA must submit a proposed REMS; the FDA will not approve the application without a REMS, if required.

Before approving an NDA or a BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA or a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical studies were conducted in compliance with IND study requirements and GCP requirements. To assure GMP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production, and quality control.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the NDA or BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical studies are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the agency decides not to approve the marketing application, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the application identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical studies. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the NDA or BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a risk management plan, or otherwise limit the scope of any approval. In addition, the FDA may require post-approval clinical studies, sometimes referred to as Phase 4 clinical studies, designed to further assess a product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

One of the performance goals agreed to by the FDA under the PDUFA is to complete its review of 90% of standard NDAs and BLAs within ten months from filing and 90% of priority NDAs and BLAs within six months from filing, whereupon a review decision is to be made. The FDA does not always meet its PDUFA goal dates and its review goals are subject to change from time to time. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the application sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

#### Fast Track Designation

The FDA has various programs, including Fast Track, which are intended to expedite the process for reviewing drugs. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification. Generally, drugs that are eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs, and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to expedite the FDA's review of drugs that treat serious or life-threatening diseases or conditions and fill unmet medical needs. Under the Fast Track process, drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists, may also receive priority review by the FDA, or review within six months of the filing of an NDA compared to a traditional review time of ten months. Although Fast Track and priority review do not affect the standards for approval of a drug, for Fast Track designated drugs, the FDA will also attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug, to expedite such drug's review and development. Although FDA has granted fast track designations to TV-45070 for EM and to Glybera for LPLD, such designations may not result in a faster development or review time, do not increase the odds of approval, and may be rescinded at any time if these drug candidates do not continue to meet the qualifications for these programs.

#### Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the U.S., or more than 200,000 individuals in the U.S. and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the U.S. for this type of disease or condition will be

recovered from sales of the product. Both Glybera and TV-45070 have received orphan drug designation from the FDA. Orphan product designation must be requested before submitting an NDA or BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for such drug for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the EU has similar, but not identical, benefits, including up to ten years of exclusivity.

### Post-Approval Requirements

Maintaining substantial compliance with applicable federal, provincial, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of drug and biological products continues after approval, particularly with respect to GMP. We will rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the GMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to drug and biological products, include reporting of GMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After an NDA or BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of drug and biological products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Drug and biological product manufacturers and other entities involved in the manufacture and distribution of approved drug or biological products are required to register their establishments with the FDA and certain state agencies, and

are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMPs and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain GMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA or BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

### U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA or BLA plus the time between the submission date of an NDA or BLA and the approval of that application. Only one patent applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration.

Under the Hatch-Waxman Amendments, a drug product containing a new chemical entity as its active ingredient is entitled to five years of market exclusivity, and a product for which the sponsor is required to generate new clinical data is entitled to three years of market exclusivity. A drug or biological product can also obtain pediatric market exclusivity in the U.S. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical study or studies. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biologic is granted 12 years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitted under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) 18 months after approval if there is no legal challenge, (iii) 18 months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

### Additional Regulation

In addition to the foregoing, provincial, state and federal U.S. and Canadian laws regarding environmental protection and hazardous substances affect our business. 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. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws



and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

U.S. Foreign Corrupt Practices Act and Canadian Corruption of Foreign Public Officials Act

The U.S. Foreign Corrupt Practices Act and the Canadian Corruption of Foreign Public Officials Act, to which we are subject, prohibit corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. We can also be held liable for the acts of our third party agents under the Canadian Corruption of Foreign Public Officials Act.

## Government Regulation Outside of the U.S.

In addition to regulations in the U.S., we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the U.S. have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the EU, for example, a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country's requirements, clinical study development may proceed.

The requirements and process governing the conduct of clinical studies, product licensing, coverage, pricing and reimbursement vary from country to country. In all cases, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational drug or biological product under EU regulatory systems, we must submit a marketing authorization application, or MAA. The application used to file the NDA or BLA in the U.S. is similar to that required in the EU, with the exception of, among other things, country-specific document requirements. The EU also provides opportunities for market exclusivity. For example, in the EU, upon receiving marketing authorization, new chemical entities generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic application. During the additional two-year period of market exclusivity, a generic marketing authorization can be submitted, and the innovator's data may be referenced, but no generic product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the EU's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity. Products receiving orphan designation in the EU can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the EU for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the EU are similar in principle to those in the U.S. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Glybera has received orphan drug designation for the treatment of LPLD in the EU.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
  - the applicant consents to a second orphan medicinal product application; or
- the applicant cannot supply enough orphan medicinal product.

For other countries outside of the EU, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product licensing, coverage, pricing and reimbursement vary from country to country. In all cases, again, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

#### Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. In the U.S. and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the availability of coverage and adequate reimbursement from third-party payers. Third-party payers include government programs such as Medicare or Medicaid, managed care plans, private health insurers, and other organizations. These third-party payers may deny coverage or reimbursement for a product or therapy in whole or in part if they determine that the product or therapy was not medically appropriate or necessary. Third-party payers may attempt to control costs by limiting coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication, and by limiting the amount of reimbursement for particular procedures or drug treatments.

The cost of pharmaceuticals and devices continues to generate substantial governmental and third party payer interest. We expect that the pharmaceutical industry will experience pricing pressures due to the trend toward managed healthcare, the increasing influence of managed care organizations and additional legislative proposals. Third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Some third-party payers also require pre-approval of coverage for new or innovative devices or drug therapies before they will reimburse healthcare providers who use such therapies. While we cannot predict whether any proposed cost-containment measures will be adopted or otherwise implemented in the future, these requirements or any announcement or adoption of such proposals could have a material adverse effect on our ability to obtain adequate prices for our product candidates and to operate profitably.

In international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. There can be no assurance that our products will be considered medically reasonable and necessary for a specific indication, that our products will be considered cost-effective by third-party payers, that coverage or an adequate level of reimbursement will be available or that the third-party payers' reimbursement policies will not adversely affect our ability to sell our products profitably.

#### Healthcare Reform

In the U.S. and foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs.

In the U.S., the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the Medicare Modernization Act, changed the way Medicare covers and pays for pharmaceutical products. The Medicare Modernization Act expanded Medicare coverage for drug purchases by the elderly by establishing Medicare Part D

and introduced a new reimbursement methodology based on average sales prices for physician administered drugs under Medicare Part B. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class under the new Medicare Part D program. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and reimbursement rate that we receive for any of our approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payers.

In March 2010, the President signed into law the Patient Protection and Affordable Care Act, as amended, or PPACA, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against healthcare fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on pharmaceutical and medical device manufacturers and impose additional health policy reforms. Among other things, PPACA revises the definition of “average manufacturer price” for reporting purposes, which could increase the amount of Medicaid drug rebates to states. Further, the new law imposes a significant annual fee on companies that manufacture or import branded prescription drug products. Substantial new provisions affecting compliance have also been enacted, which may affect our business practices with healthcare practitioners and a significant number of provisions are not yet, or have only recently become, effective. Although it is too early to determine the full effect of PPACA, the new law appears likely to continue the downward pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

In addition, other legislative changes have been proposed and adopted since PPACA was enacted. These new laws may result in reductions in Medicare and other healthcare funding, which could have a material adverse effect on our customers and accordingly, our financial operations.

We expect that PPACA, as well as other healthcare reform measures that have been and may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product, and could seriously harm our future revenue. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products.

In addition, different pricing and reimbursement schemes exist in other countries. In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may be marketed only once a reimbursement price has been agreed upon. Some of these countries may require, as condition of obtaining reimbursement or pricing approval, the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

#### Other Healthcare Laws and Compliance Requirements

In the U.S., the research, manufacturing, distribution, sale and promotion of drug products and medical devices are potentially subject to regulation by various federal, provincial, state and local authorities in addition to the FDA, including the Centers for Medicare & Medicaid Services, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, state Attorneys General, and other state and local government agencies. For example, sales, marketing and scientific/educational grant programs must comply with fraud and abuse laws such as the federal Anti-Kickback Statute, as amended, the federal False Claims Act, as amended, and similar state laws. Pricing and rebate programs must comply with the Medicaid Drug Rebate Program requirements of the Omnibus Budget Reconciliation Act of 1990, as amended, and the Veterans Health Care Act of 1992, as amended. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. All of these activities are also potentially subject to federal and state consumer protection and unfair competition laws.



The federal Anti-Kickback Statute prohibits any person, including a prescription drug manufacturer (or a party acting on its behalf), from knowingly and willfully soliciting, receiving, offering or providing remuneration, directly or indirectly, to induce or reward either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. The term “remuneration” is not defined in the federal Anti-Kickback Statute and has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of payments, ownership interests and providing anything at less than its fair market value. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain business arrangements from prosecution, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from federal Anti-Kickback Statute liability. The reach of the Anti-Kickback Statute was broadened by the recently enacted PPACA, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the PPACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act (discussed below) or the civil monetary penalties statute, which imposes fines against any person who is determined to have presented or caused to be presented claims to a federal healthcare program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. Additionally, many states have adopted laws similar to the federal Anti-Kickback Statute, and some of these state prohibitions apply to referral of patients for healthcare items or services reimbursed by any third-party payer, not only the Medicare and Medicaid programs in at least some cases, and do not contain safe harbors.

The federal False Claims Act imposes liability on any person or entity that, among other things, knowingly presents, or causes to be presented, a false or fraudulent claim for payment by a federal healthcare program. The qui tam provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any monetary recovery. In recent years, the number of suits brought by private individuals has increased dramatically. In addition, various states have enacted false claims laws analogous to the False Claims Act. Many of these state laws apply where a claim is submitted to any third-party payer and not merely a federal healthcare program. There are many potential bases for liability under the False Claims Act. Liability arises, primarily, when an entity knowingly submits, or causes another to submit, a false claim for reimbursement to the federal government. The False Claims Act has been used to assert liability on the basis of inadequate care, kickbacks and other improper referrals, improperly reported government pricing metrics such as Best Price or Average Manufacturer Price, improper use of Medicare numbers when detailing the provider of services, improper promotion of off-label uses (i.e., uses not expressly approved by FDA in a drug’s label), and allegations as to misrepresentations with respect to the services rendered. Our future activities relating to the reporting of discount and rebate information and other information affecting federal, provincial, state and third party reimbursement of our products, and the sale and marketing of our products and our service arrangements or data purchases, among other activities, may be subject to scrutiny under these laws. We are unable to predict whether we would be subject to actions under the False Claims Act or a similar state law, or the impact of such actions. However, the cost of defending such claims, as well as any sanctions imposed, could adversely affect our financial performance. Also, the Health Insurance Portability and Accountability Act of 1996, or HIPAA, created several new federal crimes, including healthcare fraud, and false statements relating to healthcare matters. The healthcare fraud statute prohibits knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.



In addition, we may be subject to, or our marketing activities may be limited by, data privacy and security regulation by both the federal government and the states in which we conduct our business. For example, HIPAA and its implementing regulations established uniform federal standards for certain “covered entities” (healthcare providers, health plans and healthcare clearinghouses) governing the conduct of certain electronic healthcare transactions and protecting the security and privacy of protected health information. The American Recovery and Reinvestment Act of 2009, commonly referred to as the economic stimulus package, included expansion of HIPAA’s privacy and security standards called the Health Information Technology for Economic and Clinical Health Act, or HITECH. Among other things, HITECH makes HIPAA’s privacy and security standards directly applicable to “business associates”—independent contractors or agents of covered entities that create, receive, maintain, or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney’s fees and costs associated with pursuing federal civil actions.

There are also an increasing number of state “sunshine” laws that require manufacturers to make reports to states on pricing and marketing information. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. In addition, beginning in 2013, a similar federal requirement began requiring manufacturers to track and report to the federal government certain payments and other transfers of value made to physicians and other healthcare professionals and teaching hospitals and ownership or investment interests held by physicians and their immediate family members. The federal government discloses the reported information on a publicly available website. These laws may affect our sales, marketing, and other promotional activities by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities.

Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government healthcare programs, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of pre-marketing product approvals, private qui tam actions brought by individual whistleblowers in the name of the government or refusal to allow us to enter into supply contracts, including government contracts, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-approval requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

#### Environmental Matters

Our operations require the use of hazardous materials (including biological materials) which subject us to a variety of federal, provincial and local environmental and safety laws and regulations. Some of the regulations under the current regulatory structure provide for strict liability, holding a party potentially liable without regard to fault or negligence. We could be held liable for damages and fines as a result of our, or someone else’s, business operations should contamination of the environment or individual exposure to hazardous substances occur. We cannot predict how changes in laws or development of new regulations will affect our business operations or the cost of compliance.

#### Employees

As of December 31, 2015, we had 83 employees, including 76 full-time employees. Of our employees, 55 were primarily engaged in research and development, and 25 of whom hold a Ph.D. or M.D. (or equivalent) degree. None of our employees are represented by a labor union. We have not experienced any work stoppages, and we consider our relations with our employees to be good.

#### Research and Development

We have committed, and expect to continue to commit, significant resources to developing new product candidates. We have assembled experienced research and development teams at our Burnaby, British Columbia location with scientific, clinical and regulatory personnel. Our research and development expenses for the years ended

December 31, 2015, 2014, and 2013 were \$15.2 million, \$11.8 million, and \$12.3 million, respectively.

#### Manufacturing

We currently rely, and expect to continue to rely, on third parties and our collaborators for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture if our product candidates receive marketing approval. Accordingly, we have not internally developed any manufacturing facilities or hired related personnel.

To date, we have obtained materials for our product candidates from multiple third-party manufacturers. We believe that all of the materials required for the manufacture of our product candidates can be obtained from more than one source. However, the manufacturing processes for each of our product candidates, which include large and small-molecules, vary and sourcing adequate supplies may be made more difficult depending on the type of product candidate involved. Our small-molecule product candidates generally can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. This chemistry generally is amenable to scale-up and does not require unusual equipment in the manufacturing process.

## Corporate Information

We were incorporated in the Province of British Columbia on November 5, 1996 under the predecessor to the Business Corporations Act (British Columbia) under the name “Xenon Bioresearch Inc.” We continued from British Columbia to the federal jurisdiction pursuant to Section 187 of the Canada Business Corporations Act, or the CBCA, on May 17, 2000 and concurrently changed our name to “Xenon Genetics Inc.” We registered as an extra-provincial company in British Columbia on July 10, 2000 and changed our name to “Xenon Pharmaceuticals Inc.” on August 24, 2004. We have no subsidiaries. Our principal executive offices are located at 200 – 3650 Gilmore Way, Burnaby, British Columbia, Canada V5G 4W8, and our telephone number is (604) 484-3300. We are a reporting issuer in British Columbia, Alberta and Ontario, but our shares are not listed on any recognized Canadian stock exchange. Our common shares trade on The NASDAQ Global Market under the symbol “XENE.”

## Where You Can Find Additional Information

We make available free of charge through our investor relations website, <http://www.xenon-pharma.com>, our annual reports, quarterly reports, current reports, proxy statements and all amendments to those reports as soon as reasonably practicable after such material is electronically filed or furnished with the SEC. These reports may also be obtained without charge by contacting Investor Relations, Xenon Pharmaceuticals Inc., 200 – 3650 Gilmore Way, Burnaby, British Columbia, Canada V5G 4W8, e-mail: [investors@xenon-pharma.com](mailto:investors@xenon-pharma.com). Our Internet website and the information contained therein or incorporated therein are not intended to be incorporated into this Annual Report on Form 10-K. In addition, the public may read and copy any materials we file or furnish with the SEC at the SEC’s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549 or may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. Moreover, the SEC maintains an Internet site that contains reports, proxy and information statements, and other information regarding reports that we file or furnish electronically with them at [www.sec.gov](http://www.sec.gov). Additional information related to Xenon is also available on SEDAR at [www.sedar.com](http://www.sedar.com).

## Item 1A. Risk Factors

You should carefully consider the following risk factors, in addition to the other information contained in this report, including the section of this report captioned “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our financial statements and related notes. If any of the events described in the following risk factors and the risks described elsewhere in this report occurs, our business, operating results and financial condition could be seriously harmed. This report on Form 10-K also contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in the forward-looking statements as a result of factors that are described below and elsewhere in this report.

## Risks Related to Our Financial Condition and Capital Requirements

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

We are a clinical-stage biotechnology company and, other than the years ended December 31, 2014 and 2013, we have recorded net losses in each annual reporting period since inception in 1996, and we do not expect to have sustained profitability for the foreseeable future. We had net losses of \$15.8 million for the year ended December 31, 2015 and an accumulated deficit of \$119.7 million as of December 31, 2015.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. To date, we have financed our operations through the sale of equity securities, funding received from our licensees and collaborators and, to a lesser extent, government funding. Other than royalties we are eligible to receive from sales of Glybera under our license to uniQure Biopharma B.V., or uniQure, we have not generated any royalty revenue from product sales and our product candidates will require substantial additional investment before they will provide us with any product royalty revenue.

We expect to incur significant expenses and increasing operating losses for the foreseeable future as we:

- continue our research and preclinical and clinical development of our product candidates;
- expand the scope of our clinical studies for our current and prospective product candidates;
- initiate additional preclinical, clinical or other studies for our product candidates, including under our collaboration agreements;
  - change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical studies;

- seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- make milestone or other payments under our in-license agreements including, without limitation, our agreements with the University of British Columbia, or UBC, and the Memorial University of Newfoundland;
- maintain, protect and expand our intellectual property portfolio;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we or one of our collaborators may obtain marketing approval, and for which we have maintained commercial rights;
  - create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above.

Our expenses could increase beyond expectations for a variety of reasons, including if we are required by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory agencies, domestic or foreign, to perform clinical and other studies in addition to those that we currently anticipate. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our shareholders' equity.

Other than royalties we are eligible to receive from sales of Glybera, we have not generated any royalty revenue from product sales and may never become profitable on a U.S. GAAP basis.

Our ability to generate meaningful revenue and achieve profitability on a U.S. GAAP basis depends on our ability, alone or with strategic collaborators, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our product candidates. Substantially all of our revenue since inception has consisted of upfront and milestone payments associated with our collaboration and license agreements. Revenue from these agreements is dependent on successful development of our product candidates by us or our collaborators. Other than royalties we are eligible to receive from sales of Glybera under our license to uniQure, we have not generated any royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales for the foreseeable future, if ever. Commercial sales of Glybera commenced in November 2015, but we do not expect to receive significant revenue in the near-term from these sales. If any of our product candidates fail in clinical trials or do not gain regulatory approval, or if Glybera or any of our future products, if any, once approved, fail to achieve market acceptance or adequate market share, we may never become profitable. Although we were profitable for the years ended December 31, 2014 and 2013, we may not be able to sustain profitability in subsequent periods. Our ability to generate future revenue from product sales depends heavily on our success, and the success of our collaborators, in:

- completing research, preclinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- commercializing products for which we obtain regulatory and marketing approval, either with a collaborator or, if launched independently, by establishing sales, marketing and distribution infrastructure;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;
- obtaining market acceptance of products for which we obtain regulatory and marketing approval as therapies;
- addressing any competing technological and market developments;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for any approved products in the future;
- developing sustainable, scalable, reproducible, and transferable manufacturing processes for any of our products approved in the future;
- maintaining, protecting, expanding and enforcing our portfolio of intellectual property rights, including patents, trade secrets and know-how;

- implementing additional internal systems and infrastructure, as needed; and
- attracting, hiring and retaining qualified personnel.

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The scope of our future revenue will also depend upon the size of any markets in which our product candidates receive approval and the availability of insurance coverage and the availability and amount of reimbursement from third-party payers for Glybera and future products, if any. If we are unable to achieve sufficient revenue to become profitable and remain so, our financial condition and operating results will be negatively impacted, and our trading price might be harmed.

We will likely need to raise additional funding, which may not be available on acceptable terms, if at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

Since our inception, we have dedicated most of our resources to the discovery and development of our proprietary preclinical and clinical product candidates, and we expect to continue to expend substantial resources doing so for the foreseeable future. These expenditures will include costs associated with research and development, manufacturing of product candidates and products approved for sale, conducting preclinical experiments and clinical trials and obtaining and maintaining regulatory approvals, as well as commercializing any products later approved for sale. During the year ended December 31, 2015, we incurred approximately \$15.2 million of costs associated with research and development, exclusive of costs incurred by our collaborators in developing our product candidates.

Our current cash and cash equivalents and marketable securities are not expected to be sufficient to complete clinical development of any of our product candidates and prepare for commercializing any product candidate which receives regulatory approval. Accordingly, we will likely require substantial additional capital to continue our clinical development and potential commercialization activities. Our future capital requirements depend on many factors, including but not limited to:

- the number and characteristics of the future product candidates we pursue;
  - the scope, progress, results and costs of independently researching and developing any of our future product candidates, including conducting preclinical research and clinical trials;
- whether our existing collaborations continue to generate substantial milestone payments and, ultimately, royalties on future approved products for us;
- the timing of, and the costs involved in, obtaining regulatory approvals for any future product candidates we develop independently;
- the cost of future commercialization activities, including activities required pursuant to our option to co-promote TV-45070, if exercised by us, and the cost of commercializing any future products we develop independently that are approved for sale;
- the cost of manufacturing our future product candidates and products, if any;
  - our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such agreements;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patents, including litigation costs and the outcome of such litigation; and
- the timing, receipt and amount of sales of, or royalties on, Glybera, and our future products, if any.

We are unable to estimate the funds we will actually require to complete research and development of our product candidates or the funds required to commercialize any resulting product in the future.

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that our existing cash and cash equivalents and marketable securities as of the date of this report and research funding that we expect to receive under our existing collaborations, will enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 to 24 months.



Our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. Raising funds in the future may present additional challenges and future financing may not be available in sufficient amounts or on terms acceptable to us, if at all.

Raising additional capital may cause dilution to our existing shareholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

The terms of any financing arrangements we enter into may adversely affect the holdings or the rights of our shareholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our shareholders. The incurrence of indebtedness would result in increased fixed payment obligations and, potentially, the imposition of restrictive covenants. Those covenants may include limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborators or otherwise at an earlier stage than otherwise would be desirable resulting in the loss of rights to some of our product candidates or other unfavorable terms, any of which may have a material adverse effect on our business, operating results and prospects. In addition, any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates.

Unstable market and economic conditions may have serious adverse consequences on our business and financial condition.

Global credit and financial markets experienced extreme disruptions at various points over the last decade, characterized by diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. If another such disruption in credit and financial markets and deterioration of confidence in economic conditions occurs, our business may be adversely affected. If the equity and credit markets were to deteriorate significantly in the future, it may make any necessary debt or equity financing more difficult to complete, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon development or commercialization plans. In addition, there is a risk that one or more of our current collaborators, service providers, manufacturers and other partners would not survive or be able to meet their commitments to us under such circumstances, which could directly affect our ability to attain our operating goals on schedule and on budget.

We are subject to risks associated with currency fluctuations which could impact our results of operations.

As of December 31, 2015, approximately 70% of our cash and cash equivalents and marketable securities was denominated in Canadian dollars. Historically, the majority of our operating expenses have been denominated in Canadian dollars and the majority of our revenue has been denominated in U.S. dollars and we expect this trend to continue.

Prior to December 31, 2014, our functional currency was the Canadian dollar. On January 1, 2015, our functional currency changed from the Canadian dollar to the U.S. dollar based on our analysis of the changes in the primary economic environment in which we operate. As a result, changes in the exchange rate between the Canadian dollar and the U.S. dollar could materially impact our reported results of operations and distort period to period comparisons. In particular, to the extent that foreign currency-denominated (i.e., non-U.S. dollar) monetary assets do not equal the amount of our foreign currency denominated monetary liabilities, foreign currency gains or losses could arise and materially impact our financial statements. As a result of such foreign currency fluctuations, it could be more difficult to detect underlying trends in our business and results of operations. In addition, to the extent that fluctuations in currency exchange rates cause our results of operations to differ from our expectations or the expectations of our investors, the trading price of our common shares could be adversely affected.

From time to time, we may engage in exchange rate hedging activities in an effort to mitigate the impact of exchange rate fluctuations. For example, we maintain a natural currency hedge against fluctuations in the U.S./Canadian foreign exchange rate by matching the amount of U.S. dollar and Canadian dollar investments to the expected amount of future U.S. dollar and Canadian dollar obligations, respectively. Any hedging technique we implement may fail to be effective. If our hedging activities are not effective, changes in currency exchange rates may have a more significant impact on the trading price of our common shares.

## Risks Related to Our Business

We, or our collaborators, may fail to successfully develop our product candidates.

Our product candidates, including TV-45070, GDC-0276, GDC-0310 and XEN801, and compounds in our preclinical and discovery pipeline, are in varying stages of development and will require substantial clinical development, testing and regulatory approval prior to commercialization. It may be several more years before these product candidates or any of our other product candidates receive marketing approval, if ever. If any of our product candidates fail to become approved products, our business, growth prospects, operating results and financial condition may be adversely affected and a decline of our common share price could result. For example, in July 2015, we and our partner Teva Pharmaceutical Industries Ltd., or Teva, announced top line results from a Phase 2b study designed to evaluate the safety and efficacy of topically applied TV-45070 in patients with chronic pain due to osteoarthritis, or OA, of the knee. Results from this trial showed that TV-45070 did not demonstrate statistically significant difference from placebo in efficacy endpoints of reductions in pain due to OA and neither we nor Teva have plans for further development of TV-45070 in OA, although clinical development of TV-45070 in post-herpetic neuralgia, or PHN, continues.

Our near-term operating revenue is partially dependent upon the regulatory and marketing efforts of uniQure, or its sublicensee, for the development and commercialization of Glybera.

Under the terms of our license agreement with uniQure, we rely on uniQure, or its sublicensees, to market Glybera and to obtain and maintain regulatory approval of Glybera. In July 2013, uniQure announced that it had granted to Chiesi Farmaceutici, S.p.A., or Chiesi, an Italian pharmaceutical firm, an exclusive license to commercialize Glybera in the European Union, or the EU, and certain other countries outside of North America and Japan. Commercial sales of Glybera commenced in November 2015. Despite the efforts of uniQure and Chiesi, Glybera may not gain market acceptance among physicians, patients, healthcare payers and the medical community. The commercial success of Glybera will depend on a number of factors, including:

- establishment and demonstration of clinical efficacy and safety and acceptance of the same by the medical community and regulatory authorities;
- commercialization of competing products;
- sufficient commercial supply of Glybera;
- cost-effectiveness of Glybera;
- regulatory authorities' final assessment of the benefit-risk analysis of Glybera;
- the availability of coverage and adequate reimbursement from third parties, including governmental payers, managed care organizations, and private health insurers;
- the relative cost, safety and efficacy of therapies that exist now or may be developed in the future;
- whether the product can be manufactured in commercial quantities at acceptable cost;
- marketing and distribution support for Glybera;
- cost of post-approval obligations in the EU including a post-approval clinical trial and market surveillance activities;
- maintaining the marketing approval under exceptional circumstances in the EU;
- the effect of current and future healthcare laws;
- the acceptance of gene therapies as a class of treatment; and
- any market or regulatory exclusivities applicable to the product.

Glybera is approved in the EU under exceptional circumstances and full approval may never be granted or the existing approval under exceptional circumstances could be revoked. As a condition to approval of Glybera, uniQure is required to complete a post-approval clinical trial and is required to implement a disease registry as well as implement risk management procedures, distribute educational materials to healthcare professionals and patients, implement an additional manufacturing process step, comply with certain notification obligations and undergo annual reassessment,

any negative outcome of which could potentially lead to a withdrawal of marketing approval for Glybera.

Any failure of uniQure or its sublicensee to successfully commercialize Glybera or revocation of Glybera's marketing approval in the EU could have a material adverse effect on our business, growth prospects, operating results and financial condition and could result in a substantial decline in the price of our common shares.

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We and our collaborators face substantial competition in the markets for our product candidates, which may result in others discovering, developing or commercializing products before us or doing so more successfully than we or our collaborators do.

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We face potential competition in target discovery and product development from many different approaches and sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we or our collaborators successfully develop and commercialize will compete with existing products and any new products that may become available in the future.

The key competitive factors affecting the success of all of our product candidates, if approved, are likely to be their efficacy, safety, convenience and price; the effectiveness and safety of alternative products; the level of generic competition; and the availability of coverage and adequate reimbursement from government and other third-party payers.

With respect to target discovery activities, competitors and other third parties, including academic and clinical researchers, may access rare families and identify novel targets for drug development before we do.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we, or our collaborators, do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early stage companies may also prove to be significant competitors, particularly through collaboration arrangements with large and established companies.

Our commercial opportunities could be reduced or eliminated if our competitors develop and commercialize products or therapies that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected by decisions made by insurers or other third party payers.

To the extent that we are unable to compete effectively against one or more of our competitors in these areas, our business will not grow and our financial condition, results of operations and common share price may suffer.

There are no approved gene therapies currently on the market for lipoprotein lipase deficiency, or LPLD, in the U.S. The current management of LPLD consists of strict adherence to an extremely low-fat diet, but compliance with such a diet is challenging. Lipid-lowering drugs are generally not effective for treating LPLD. We are not aware of any other drugs or therapies currently in development that treat LPLD by using the lipoprotein lipase, or LPL, sequence containing the LPL<sup>S447X</sup> genetic variant or otherwise.

Drug discovery and development for various pain applications is intensely competitive. There are a large number of approved products for neuropathic pain, inflammatory pain and other pain indications. These approved products include capsaicin, celecoxib, lidocaine, narcotic analgesics and pregabalin. We are also aware of clinical-stage development programs at several pharmaceutical and biotechnology companies that are developing Nav1.7 inhibitors or other sodium channel inhibitors for the treatment of pain, including Biogen Inc., Dainippon Sumitomo Co., Ltd., Eli Lilly and Company, Merck & Co., Inc., or Merck, NeuroQuest Inc., and Vertex Pharmaceuticals Inc. Moreover,

we are aware of various other product candidates in development that target other mechanisms of action to treat various pain indications, including calcium channel inhibitors, nerve growth factor inhibitors and P2X purinoceptor 3 inhibitors.

If XEN801 were approved for the treatment of acne, we anticipate it would compete with other approved prescription acne products including topical retinoids, oral hormonal therapies, topical and oral antimicrobials, and oral isotretinoin. In addition to approved prescription therapies, there are a wide range of over-the-counter, or OTC, treatments targeted at treating acne. Additionally, there are a number of prescription products that are used “off-label” for the treatment of acne. We are also aware of several products in clinical development that could potentially compete with XEN801, including products in development from Allergan PLC, AOBiome LLC, Braintree Laboratories Inc., Cassiopea SpA, Dermira Inc., Foamix Pharmaceuticals Ltd., Galderma SA, Mimetica Pty Ltd, Novan Therapeutics, Phosphagenics Ltd, Valeant Pharmaceuticals, and XBiotech Inc.

The novelty of gene therapy products and their lack of a commercial track record may hinder market acceptance of Glybera among physicians, patients, healthcare payers and the medical community.

Glybera is the first gene therapy product approved in the EU, and no gene therapy product has been approved in the U.S. Because Glybera is the first gene therapy to be marketed in the EU, gaining market acceptance and overcoming any safety or efficacy concerns may be more challenging than for a more traditional therapy. Glybera's commercial success will depend, in part, on the success of efforts to educate the market regarding gene therapy products. In particular, the success of Glybera will depend upon physicians who treat patients with LPLD, prescribing Glybera. With respect to Glybera and any other gene therapy products we or a collaborator may develop, public perception may be influenced by claims that gene therapy is unsafe, and, if so, gene therapy may not gain the acceptance of the public or the medical community.

We have no marketed products and have not yet advanced a product candidate beyond Phase 2 clinical trials, which makes it difficult to assess our ability to develop our future product candidates and commercialize any resulting products independently.

We have no experience in Phase 3 and later stage clinical development, and related regulatory requirements or the commercialization of products. uniQure controls and has been responsible for the development and commercialization of Glybera, Teva is responsible for the on-going clinical development of TV-45070, and Genentech Inc., or Genentech, is responsible for the on-going clinical development of GDC-0276 and GDC-0310. Accordingly, we have not yet demonstrated our ability to independently and repeatedly conduct clinical development after Phase 2, obtain regulatory approval and commercialize therapeutic products. We will need to develop such abilities if we are to execute on our business strategy to selectively develop and independently commercialize product candidates for orphan and niche indications. To execute on our business plan for the development of independent programs, we will need to successfully:

- execute our clinical development plans for later-stage product candidates;
- obtain required regulatory approvals in each jurisdiction in which we will seek to commercialize products;
- build and maintain appropriate sales, distribution and marketing capabilities;
- gain market acceptance for our future products, if any; and
- manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization activities.

If we are unsuccessful in accomplishing these objectives, we would not be able to develop and commercialize any future orphan and niche disease product candidates independently, and could fail to realize the potential advantages of doing so.

If we are not successful in leveraging our Extreme Genetics discovery platform to discover product candidates in addition to TV-45070, GDC-0276, GDC-0310 and XEN801, our ability to expand our business and achieve our strategic objectives may be impaired.

We rely on our Extreme Genetics discovery platform to identify validated drug targets and develop new product candidates. To date, our Extreme Genetics discovery platform has yielded one approved product, Glybera, and four clinical development candidates TV-45070, GDC-0276, GDC-0310 and XEN801. Use of our discovery platform requires substantial technical, financial and human resources, regardless of whether we identify any novel drug targets. Our Extreme Genetics discovery platform may initially show promise in identifying additional potential product candidates, yet fail to yield viable product candidates for clinical development or commercialization. Such failure may occur for many reasons, including the following: any product candidate may, on further study, be shown to have serious or unexpected side effects or other characteristics that indicate it is unlikely to be safe or otherwise does not meet applicable regulatory criteria; and any product candidate may not be capable of being produced in



commercial quantities at an acceptable cost, or at all.

If we are unable to identify additional product candidates suitable for clinical development and commercialization, we may not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely impact our trading price.

Our approach to drug discovery is unproven, and we do not know whether we will be able to develop any products of commercial value.

Our Extreme Genetics discovery platform may not reproducibly or cost-effectively result in the discovery of product candidates and development of commercially viable products that safely and effectively treat human disease.

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There are various challenges in utilizing our Extreme Genetics discovery platform to successfully identify novel drug targets, including locating families suffering from rare disorders and severe phenotypes, entering into agreements with foreign collaborators, complying with various domestic and foreign privacy laws, accessing required technologies in a timely manner and transporting DNA across national borders.

To date, only Glybera has been both developed using our Extreme Genetics discovery platform and approved for commercial sale. If the use of our Extreme Genetics discovery platform fails to identify novel targets for drug discovery, or such targets prove to be unsuitable for treating human disease, or we are unable to develop product candidates with specificity and selectivity for such targets, we will fail to develop viable products. If we fail to develop and commercialize viable products, we will not achieve commercial success.

We may encounter difficulties in managing our growth, including headcount, and expanding our operations successfully.

Our business strategy involves continued development and, where development is successful, commercialization of select successfully developed product candidates for orphan and niche indications independently. In order to execute on this strategy, we will need to build out a regulatory, sales, manufacturing, distribution and marketing infrastructure and expand our development capabilities or contract with third parties to provide these capabilities and infrastructure for us. To achieve this, we will need to identify, hire and integrate personnel who have not worked together as a group previously. We anticipate that we may need to hire additional accounting, legal and financial staff with appropriate public company experience and technical accounting and other knowledge to address the added burdens of operating as a newly public company. There are likely to be infrastructure costs associated with public company compliance as well.

As our operations expand, we expect that we will need to manage additional relationships with various strategic collaborators, suppliers and other third parties.

Drs. Simon Pimstone and Y. Paul Goldberg each devote a small amount of their time to clinical work outside of their duties at our company, conducting, generally, two to three outpatient clinics per month. Future growth will impose significant added responsibilities on members of management, and our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities.

If we are to effectively manage our growth, our expenses may increase more than expected, our ability to generate and grow revenue could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

If we fail to attract and retain senior management and key personnel, we may be unable to successfully develop our product candidates, perform our obligations under our collaboration agreements, conduct our clinical trials and commercialize our product candidates.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel.

We could experience difficulties attracting and retaining qualified employees as competition for qualified personnel in the biotechnology and pharmaceutical field is intense. We are highly dependent upon our senior management, particularly Dr. Pimstone, our Chief Executive Officer and President; Mr. Ian Mortimer, our Chief Financial Officer and Chief Operating Officer; and Dr. Goldberg, our Vice President, Clinical Development, as well as other

employees. In the near future, the loss of services of any of these individuals or one or more of our other members of senior management could materially delay or even prevent the successful development of our product candidates.

In addition, we will need to hire additional personnel as we expand our clinical development activities and develop commercial capabilities, including a sales infrastructure to support our independent commercialization efforts. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. The inability to recruit or loss of the services of any executive or key employee may impede the progress of our research, development and commercialization objectives.

Our employees, collaborators and other personnel may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, collaborators, vendors, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA, EMA and other non-U.S. regulators, provide accurate information to the FDA, EMA and other non-U.S. regulators, comply with data privacy and security and healthcare fraud and abuse laws and regulations in the U.S. and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. Additionally, laws regarding data privacy and security, including the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, as well as comparable laws in non-U.S. jurisdictions, may impose obligations with respect to safeguarding the privacy, use, security and transmission of individually identifiable health information such as genetic material or information we obtain through our direct-to-patient web-based recruitment approach for identifying patients with rare or extreme phenotypes.

Various laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Any misconduct could also involve the improper use of information obtained in the course of clinical studies, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

Our business and operations could suffer in the event of system failures.

Computer system, network or telecommunications failures due to events such as damage from malware, unauthorized access, terrorism, war, or natural disasters could interrupt our internal or partner operations. For example, the loss of preclinical trial data or data from completed or ongoing clinical trials for our product candidates could result in delays in our regulatory filings and development efforts and significantly increase our costs. To the extent that any disruption or security breach were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the development of our product candidates could be delayed. While we have implemented security measures and, to date, have not detected a cyber security breach nor experienced a material system failure, our internal computer systems and those of our contractors and consultants are vulnerable to damage from these events.

A variety of risks associated with international operations could materially adversely affect our business.

Glybera has been approved for commercial sale in the EU by the EMA, subject to uniQure's compliance with certain post-approval reporting and monitoring obligations. Our collaborator for TV-45070, Teva, is based in Israel and a significant portion of the research and development activities under our collaboration with Teva are performed outside of North America. If we continue to engage in significant cross-border activities, we will be subject to risks related to international operations, including:

- different regulatory requirements for maintaining approval of drugs and biologics in foreign countries;

- reduced protection for intellectual property rights in certain countries;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, political instability or open conflict in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations of doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in North America;
- likelihood of potential or actual violations of domestic and international anti-corruption laws, such as the U.S. Foreign Corrupt Practices Act and the U.K. Bribery Act, or of U.S. and international export control and sanctions regulations, which likelihood may increase with an increase of operations in foreign jurisdictions;

- tighter restrictions on privacy and the collection and use of data, including genetic material, may apply in jurisdictions outside of North America, where we find some of the families with individuals that exhibit the severe phenotypes that we study; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

If any of these issues were to occur, our business could be materially harmed.

U.S. Holders of our shares may suffer adverse tax consequences if we are characterized as a passive foreign investment company.

Generally, for any taxable year in which 75% or more of our gross income is passive income, or at least 50% of the average quarterly value of our assets (which may be determined in part by the market value of our common shares, which is subject to change) are held for the production of, or produce, passive income, we would be characterized as a passive foreign investment company, or PFIC, for U.S. federal income tax purposes. Based on the composition of our gross income and gross assets and the nature of our business, we do not believe that we were a PFIC for the taxable years ended December 31, 2015 and 2014, although we could be a PFIC in one or more subsequent years. Our status as a PFIC is a fact-intensive determination made on an annual basis and we cannot provide any assurance regarding our PFIC status for future taxable years.

If we are a PFIC for any subsequent year, U.S. Holders of our common shares may suffer adverse tax consequences. Gains realized by non-corporate U.S. Holders on the sale of our common shares would be taxed as ordinary income, rather than as capital gain, and the preferential tax rate applicable to dividends received on our common shares would be lost. Interest charges would also be added to taxes on gains and dividends realized by all U.S. Holders.

A U.S. Holder may avoid these adverse tax consequences by timely making a qualified electing fund election. For each year that we would meet the PFIC gross income or asset test, an electing U.S. Holder would be required to include in gross income its pro rata share of our net ordinary income and net capital gains, if any. A U.S. Holder may make a qualified electing fund election only if we commit to provide U.S. Holders with their pro rata share of our net ordinary income and net capital gains. If we are a PFIC in the current or a future tax year, we will provide our U.S. Holders with the information that is necessary in order for them to make a qualified electing fund election and to report their common shares of ordinary earnings and net capital gains for each year for which we are a PFIC.

A U.S. Holder may also mitigate the adverse tax consequences if we are a PFIC by timely making a mark-to-market election. Generally, for each year that we would meet the PFIC gross income or asset test, an electing U.S. Holder would include in gross income the increase in the value of its shares during each of its taxable years and deduct from gross income the decrease in the value of such shares during each of its taxable years. A mark-to-market election may be made and maintained only if our common shares are regularly traded on a qualified exchange, including The NASDAQ Global Market, or NASDAQ. Whether our common shares are regularly traded on a qualified exchange is an annual determination based on facts that, in part, are beyond our control. Accordingly, a U.S. Holder might not be eligible to make a mark-to-market election to mitigate the adverse tax consequences if we are characterized as a PFIC.

We may become subject to income tax in jurisdictions in which we are organized or operate, including the United States, which would reduce our future earnings.

There is a risk that we may become subject to income tax in jurisdictions outside of Canada, including the United States, if under the laws of any such jurisdiction, we are considered to be carrying on a trade or business there or earn income that is considered to be sourced there and we do not qualify for an exemption. In jurisdictions where we do not believe we are subject to tax, we can provide no certainty that tax authorities in those jurisdictions will not subject one or more tax years to examination. Tax examinations are often complex as tax authorities may disagree with the

treatment of items reported by us, the result of which could have a material adverse effect on our operating results and financial condition.

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Acquisitions or joint ventures could disrupt our business, cause dilution to our shareholders and otherwise harm our business.

We actively evaluate various strategic transactions on an ongoing basis and may acquire other businesses, products or technologies as well as pursue strategic alliances, joint ventures or investments in complementary businesses. Any of these transactions could be material to our financial condition and operating results and expose us to many risks, including:

- disruption in our relationships with collaborators or suppliers as a result of such a transaction;
- unanticipated liabilities related to acquired companies;
- difficulties integrating acquired personnel, technologies and operations into our existing business;
- retention of key employees;
- diversion of management time and focus from operating our business to management of strategic alliances or joint ventures or acquisition integration challenges;
- increases in our expenses and reductions in our cash available for operations and other uses; and
- possible write-offs or impairment charges relating to acquired businesses.

Foreign acquisitions involve unique risks in addition to those mentioned above, including those related to integration of operations across different cultures and languages, currency risks and the particular economic, political and regulatory risks associated with specific countries.

Also, the anticipated benefit of any strategic alliance, joint venture or acquisition may not materialize. Future acquisitions or dispositions could result in potentially dilutive issuances of our equity securities, the incurrence of debt, contingent liabilities or amortization expenses or write-offs of goodwill, any of which could harm our financial condition. We cannot predict the number, timing or size of future joint ventures or acquisitions, or the effect that any such transactions might have on our operating results.

#### Risks Related to Development, Clinical Testing and Regulatory Approval of Our Product Candidates

The regulatory approval processes of the FDA, EMA and regulators in other jurisdictions are lengthy, time-consuming and inherently unpredictable. If we, or our collaborators, are unable to obtain timely regulatory approval for our product candidates, our business will be substantially harmed.

The regulatory approval process is expensive and the time required to obtain approval from the FDA, EMA or other regulatory authorities in other jurisdictions to sell any product is uncertain and may take years. Whether regulatory approval will be granted is unpredictable and depends upon numerous factors, including the substantial discretion of the regulatory authorities. Approval policies, regulations, or the type and amount of preclinical and clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. Other than for Glybera in the EU, neither we nor our collaborators have obtained regulatory approval for any of our product candidates. It is possible that none of our existing product candidates or any of our future product candidates will ever obtain regulatory approval, even if we expend substantial time and resources seeking such approval.

Our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA, EMA or other regulatory authorities may disagree with the design or implementation of our or our collaborators' clinical trials;
- we or our collaborators may be unable to demonstrate to the satisfaction of the FDA, EMA or other regulatory authorities that a product candidate is safe and effective for its proposed indication;
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the results of clinical trials may not meet the level of statistical significance required by the FDA, EMA or other regulatory authorities for approval;

- we, or our collaborators, may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA, EMA or other regulatory authorities may disagree with our or our collaborators' interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a New Drug Application, or NDA, or other submission or to obtain regulatory approval in the U.S. or elsewhere;

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- the FDA, EMA or other regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we or our collaborators contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, EMA or other regulatory authorities outside of the U.S. may significantly change in a manner rendering our or our collaborators' clinical data insufficient for approval.

Even if we, or our collaborators, obtain approval for a particular product, regulatory authorities may grant approval contingent on the performance of costly post-approval clinical trials, or may approve a product with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product.

Clinical drug development involves a lengthy and expensive process with uncertain timelines and uncertain outcomes. If clinical trials are prolonged or delayed, we, or our collaborators, may be unable to commercialize our product candidates on a timely basis.

Clinical testing of product candidates is expensive and, depending on the stage of development, can take a substantial period of time to complete. Clinical trial outcomes are inherently uncertain, and failure can occur at any time during the clinical development process.

Clinical trials can be halted or delayed for a variety of reasons, including those related to:

- side effects or adverse events in study participants presenting an unacceptable safety risk;
- inability to reach agreement with prospective contract research organizations, or CROs, and clinical trial sites, or the breach of such agreements;
- failure of third-party contractors, such as CROs, or investigators to comply with regulatory requirements;
- delay or failure in obtaining the necessary approvals from regulators or institutional review boards, or IRBs, in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;
- a requirement to undertake and complete additional preclinical studies to generate data required to support the submission of an NDA;
- inability to enroll sufficient patients to complete a protocol, particularly in orphan diseases;
- difficulty in having patients complete a trial or return for post-treatment follow-up;
  - clinical sites deviating from trial protocol or dropping out of a trial;
- problems with drug product or drug substance storage and distribution;
- adding new clinical trial sites;
- our inability to manufacture, or obtain from third parties, adequate supply of drug substance or drug product sufficient to complete our preclinical studies and clinical trials; and
- governmental or regulatory delays and changes in regulatory requirements, policy and guidelines.

The results of any Phase 3 or other pivotal clinical trial may not be adequate to support marketing approval. These clinical trials are lengthy and, with respect to non-orphan indications, usually involve many hundreds to thousands of patients. In addition, if the FDA, EMA or another applicable regulator disagrees with our or our collaborator's choice of the key testing criterion, or primary endpoint, or the results for the primary endpoint are not robust or significant relative to the control group of patients not receiving the experimental therapy, such regulator may refuse to approve our product candidate in the region in which it has jurisdiction. The FDA, EMA or other applicable non-U.S. regulators also may require additional clinical trials as a condition for approving any of these product candidates.

We could also encounter delays if a clinical trial is suspended or terminated by us, by our collaborators, by the IRBs of the institutions in which such trial is being conducted, by any Data Safety Monitoring Board for such trial, or by the FDA, EMA or other regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA, EMA or other regulatory authorities resulting in the imposition of a clinical hold, product candidate manufacturing problems, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. In addition, delays can occur due to safety concerns arising from trials or other clinical data regarding another company's product candidate in the same compound class as one of ours.

If we or our collaborators experience delays in the completion of, or termination of, any clinical trial of one of our product candidates, the commercial prospects of the product candidate will be harmed, could shorten the patent protection period during which we may have the exclusive right to commercialize our products and our or our collaborators' ability to commence product sales and generate product revenue from the product will be delayed. In addition, any delays in completing our clinical trials will increase our costs and slow down our product candidate development and approval process. Any of these occurrences may harm our business, financial condition and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Our TV-45070, GDC-0276 and GDC-0310 product candidates for treatment of pain and XEN801 product candidate for the treatment of acne target novel molecular mechanisms. Regulatory authorities may require more extensive studies of the long-term effects of such product candidates for regulatory approval, which could delay development of our product candidates or our future product candidates based on novel mechanisms.

Our clinical trials may fail to demonstrate adequately the safety and efficacy of our product candidates, which could prevent or delay regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of our products, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that the product candidate is both safe and effective for use in each target indication. Clinical trials often fail to demonstrate safety and efficacy of the product candidate studied for the target indication. Most product candidates that commence clinical trials are never approved as products. For example, in July 2015, we and our partner Teva announced top line results from a Phase 2b study designed to evaluate the safety and efficacy of topically applied TV-45070 in patients with chronic pain due to OA of the knee. Results from this trial showed that TV-45070 did not demonstrate statistically significant difference from placebo in efficacy endpoints of reductions in pain due to OA and neither we nor Teva have plans for further development of TV-45070 in OA, although clinical development of TV-45070 in PHN continues.

In the case of some of our product candidates, we are seeking to develop treatments for diseases for which there is relatively limited clinical experience, and, in some cases our clinical trials use novel end points and measurement methodologies or subjective patient feedback, which adds a layer of complexity to our clinical trials and may delay regulatory approval. In addition, our focus on orphan and niche markets may cause us to select target indications that are in more challenging therapeutic areas. For example, clinical trials for pain, the indication for which TV-45070, GDC-0276 and GDC-0310 are being developed, are inherently difficult to conduct. The primary measure of pain is subjective patient feedback, which can be influenced by factors outside of our control, and can vary widely from day to day for a particular patient, and from patient to patient and site to site within a clinical study. The placebo effect also tends to have a more significant impact on pain trials.

If our product candidates are not shown to be both safe and effective in clinical trials, we will not be able to obtain regulatory approval or commercialize these product candidates and products. In such case, we would need to develop other compounds and conduct associated preclinical testing and clinical trials, as well as potentially seek additional financing, all of which would have a material adverse effect on our business, growth prospects, operating results, financial condition and results of operations.

We may find it difficult to enroll patients in our clinical studies, including for orphan or niche indications, which could delay or prevent clinical studies of our product candidates.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a study, to complete our clinical studies in a timely manner. Patient enrollment for clinical trials for orphan and niche indications and for more prevalent conditions is affected by factors including:

- severity of the disease under investigation;
- design of the study protocol;

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- size of the patient population;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study;
- proximity and availability of clinical study sites for prospective patients;
- availability of competing therapies and clinical studies;
- efforts to facilitate timely enrollment in clinical studies; and
- patient referral practices of physicians.

The limited patient populations in orphan and niche indications present significant recruitment challenges for clinical trials. For example, studies estimate the prevalence of LPLD to be approximately 1:1,000,000 and the prevalence of Dravet Syndrome, or DS, to be 7,500-15,000 patients in the U.S. Many of these patients may not be suitable or available for clinical trials. This means that we or our collaborators generally will have to run multi-site and potentially multi-national trials, which can be expensive and require close coordination and supervision. If we experience delays in completing our clinical trials, such delays could result in increased costs, delays in advancing our product development, delays in testing the effectiveness of our technology or termination of the clinical studies altogether.

If we fail to obtain or maintain orphan drug designation or other regulatory exclusivity for some of our product candidates, our competitive position would be harmed.

A product candidate that receives orphan drug designation can benefit from a streamlined regulatory process as well as potential commercial benefits following approval. Currently, this designation provides market exclusivity in the U.S. and the EU for seven years and ten years, respectively, if a product is the first such product approved for such orphan indication. This market exclusivity does not, however, pertain to indications other than those for which the drug was specifically designated in the approval, nor does it prevent other types of drugs from receiving orphan designations or approvals in these same indications. Further, even after an orphan drug is approved, the FDA can subsequently approve a drug with similar chemical structure for the same condition if the FDA concludes that the new drug is clinically superior to the orphan product or a market shortage occurs.

In the EU, orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria or can be lost altogether if the marketing authorization holder consents to a second orphan drug application or cannot supply enough drug, or when a second applicant demonstrates its drug is “clinically superior” to the original orphan drug. TV-45070 has received both fast track and orphan drug designations for the treatment of erythromelalgia, or EM, by the FDA. If we seek orphan drug designations for other indications or in other jurisdictions, such as for TV-45070 in the EU, we may fail to receive such orphan drug designations and, even if we succeed, such orphan drug designations may fail to result in or maintain orphan drug exclusivity upon approval, which would harm our competitive position.

Results of earlier clinical trials may not be predictive of the results of later-stage clinical trials.

The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Interpretation of results from early, usually smaller, studies that suggest a clinically meaningful response in some patients, requires caution. Results from later stages of clinical trials enrolling more patients may fail to show the desired safety and efficacy results or otherwise fail to be consistent with the results of earlier trials of the same product candidates. Later clinical trial results may not replicate earlier clinical trials for a variety of reasons, including differences in trial design, different trial endpoints (or lack of trial endpoints in exploratory studies), patient population, number of patients, patient selection criteria, trial duration, drug dosage and formulation and lack of statistical power in the earlier studies. These uncertainties are enhanced where the diseases under study lack established clinical endpoints and validated measures of efficacy, as is often the case with orphan diseases for which no drugs have been developed previously. For example, our results for two small exploratory

clinical trials for primary EM pain, one using a topical formulation and the other an oral formulation of TV-45070, used novel measures of efficacy assessment. While these studies provided promising results, further larger clinical trials will be necessary to confirm and extend these observations.

Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates are developed through preclinical to late stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and/or jeopardize our or our collaborators' ability to commence product sales and generate revenue.

Even if we obtain and maintain approval for our product candidates from one jurisdiction, we may never obtain approval for our product candidates in other jurisdictions, which would limit our market opportunities and adversely affect our business.

Sales of our approved products are, and will be, subject to U.S. and foreign regulatory requirements governing clinical trials and marketing approval, and we plan to seek regulatory approval to commercialize our product candidates in North America, the EU and in additional foreign countries. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries and regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others. For example, approval in the U.S. by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority, such as the EMA for Glybera, does not ensure approval by regulatory authorities in other countries, including by the FDA. Approval procedures vary among jurisdictions and can be lengthy and expensive, and involve requirements and administrative review periods different from, and greater than, those in the U.S., including additional preclinical studies or clinical trials. Even if our product candidates are approved, regulatory approval for any product may be withdrawn by the regulatory authorities in a particular jurisdiction.

Even if a product is approved, the FDA or the EMA, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. In many countries outside the U.S., a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for a product is also subject to approval.

Regulatory authorities in countries outside of the U.S. and the EMA also have their own requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with such foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our current and any future products, in certain countries.

If we fail to receive applicable marketing approvals or comply with the regulatory requirements in international markets, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business will be adversely affected.

We work with outside scientists and their institutions in executing our business strategy of developing product candidates using our Extreme Genetics discovery platform. These scientists may have other commitments or conflicts of interest, which could limit our access to their expertise and harm our ability to leverage our discovery platform.

We work with scientific advisors and collaborators at academic research institutions in connection with our Extreme Genetics discovery platform. These scientific advisors serve as our link to the various families with extreme

phenotypes in that these advisors may:

- identify families as potential candidates for study;
- obtain their consent to participate in our research;
- perform medical examinations and gather medical histories;
- conduct the initial analysis of suitability of the families to participate in our research based on the foregoing; and
- collect data and biological samples from the family members periodically in accordance with our study protocols.

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These scientists and collaborators are not our employees, rather they serve as either independent contractors or the primary investigators under research collaboration agreements that we have with their sponsoring academic or research institution. Such scientists and collaborators may have other commitments that would limit their availability to us. Although our scientific advisors generally agree not to do competing work, if an actual or potential conflict of interest between their work for us and their work for another entity arises, we may lose their services. It is also possible that some of our valuable proprietary knowledge may become publicly known through these scientific advisors if they breach their confidentiality agreements with us, which would cause competitive harm to our business.

#### Risks Related to Commercialization

If, in the future, we are unable to establish our own sales, marketing and distribution capabilities or enter into licensing or collaboration agreements for these purposes, we may not be successful in independently commercializing any future products.

We do not have a sales or marketing infrastructure and, as a company, have no sales, marketing or distribution experience. Our strategy involves, in part, building our own commercial infrastructure to selectively commercialize future products in niche or orphan indications. Where we believe such involvement would advance our business, we seek to retain the right to participate in the future development and commercialization of such products. For example, we have a co-promotion option for TV-45070 with Teva in the U.S.

To develop internal sales, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources, some of which will need to be committed prior to any confirmation that any of our proprietary product candidates will be approved. For any future products for which we decide to perform sales, marketing and distribution functions ourselves, we could face a number of additional risks, including:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel or develop alternative sales channels;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating and maintaining an independent sales and marketing organization.

Where and when appropriate, we may elect to utilize contract sales forces or distribution partners to assist in the commercialization of our product candidates. If we enter into arrangements with third parties to perform sales, marketing and distribution services for a product, the resulting revenue or the profitability from this revenue to us is likely to be lower than if we had sold, marketed and distributed that product ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market, and distribute our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of these third parties may fail to devote the necessary resources and attention to sell, market, and distribute our current or any future products effectively.

Even if we receive regulatory approval to commercialize any of the product candidates that we develop independently, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense.

Any regulatory approvals that we receive for our product candidates we commercialize will be subject to limitations on the approved indicated uses for which the product may be marketed or subject to certain conditions of approval, and may contain requirements for potentially costly post-approval trials, including Phase 4 clinical trials, and

surveillance to monitor the safety and efficacy of the marketed product.

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For any approved product, we will need to ensure continued compliance with extensive regulations and requirements regarding the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product. These requirements include submissions of safety and other post-approval information and reports, as well as continued compliance with current good manufacturing practices, or cGMP, and current good clinical practices, or cGCP, for any clinical trials that we or our collaborators conduct post-approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market or voluntary or mandatory product recalls;
- fines, warning letters or holds on any post-approval clinical trials;
- refusal by the FDA, EMA or another applicable regulatory authority to approve pending applications or supplements to approved applications filed by us or our collaborators, or suspension or revocation of product license approvals;
  - product seizure or detention, or refusal to permit the import or export of products;
- and
- injunctions or the imposition of civil or criminal penalties.

Occurrence of any of the foregoing could have a material and adverse effect on our business and results of operations.

If the market opportunities for any product that we or our collaborators develop are smaller than we believe they are, our revenue may be adversely affected and our business may suffer.

We intend to focus our independent product development on treatments for rare diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. Currently, most reported estimates of the prevalence of these diseases are based on studies of small subsets of the population in specific geographic areas, which are then extrapolated to estimate the prevalence of the diseases in the U.S. or elsewhere. For example, studies estimate the prevalence of LPLD to be approximately 1:1,000,000, and the prevalence of DS to be 7,500-15,000 patients in the U.S. These estimates may prove to be incorrect. If the prevalence of such diseases is smaller than we have projected, then, even if our products are approved, we may not be able to successfully commercialize them.

Even if we or our collaborators receive approval to commercialize our products, unfavorable pricing regulations and challenging third-party coverage and reimbursement practices could harm our business.

Our or any collaborators' ability to commercialize any products successfully will depend, in part, on the extent to which coverage and reimbursement for these products and related treatments will be available from government healthcare programs, private health insurers, managed care plans, and other organizations. Government authorities and third-party payers, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry is cost containment. Government authorities and third-party payers have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payers are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for any product that we or any collaborator commercialize and, if reimbursement is available, the level of reimbursement. In addition, coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we or a collaborator obtains marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we or our collaborators may not be able to successfully commercialize any product candidate for which marketing approval is obtained.



There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA, EMA or other regulatory authorities. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also be insufficient to cover our and any collaborator's costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payers and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Third-party payers often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our or any collaborator's inability to promptly obtain coverage and profitable payment rates from both government-funded and private payers for any approved products that we or our collaborators develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Our target patient populations in orphan and niche indications, where we intend to selectively develop and commercialize products independently, are relatively small. In order for therapies that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such therapies needs to be higher, on a relative basis, to account for the lack of volume. Accordingly, we will need to implement a coverage and reimbursement strategy for any approved product that accounts for the smaller potential market size. If we are unable to establish or sustain coverage and adequate reimbursement for our current and any future products from third party payers or the government, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those products.

Recently enacted and future legislation may increase the difficulty and cost for us to commercialize any products that we or our collaborators develop and affect the prices we may obtain.

The U.S. and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell any of our products profitably, once such products are approved for sale. Among policy makers and payers in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively, PPACA, was enacted in 2010 and includes measures that have significantly changed, or will significantly change, the way healthcare is financed by both governmental and private insurers. Among the provisions of PPACA of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, that began in 2011;
- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23% and 13% of the average manufacturer price for branded and generic drugs, respectively;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
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extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

· expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the Federal Poverty Level beginning in 2014, thereby potentially increasing manufacturers' Medicaid rebate liability;

· expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

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- new requirements under the federal Open Payments program, created under Section 6002 of the PPACA and its implementing regulations that manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) report annually to the U.S. Department of Health and Human Services, or HHS, information related to "payments or other transfers of value" made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals and that applicable manufacturers and applicable group purchasing organizations report annually to the HHS ownership and investment interests held by physicians (as defined above) and their immediate family members, with data collection required beginning August 1, 2013 and reporting to the Centers for Medicare & Medicaid Services, or CMS, required by the 90th day of each subsequent calendar year, and disclosure of such information made on a publicly available website starting September 2014;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians, effective in 2012;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- a licensure framework for follow-on biologic products;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- creation of the Independent Payment Advisory Board which, beginning in 2014, has authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs and those recommendations could have the effect of law even if Congress does not act on the recommendations; and
- establishment of a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending, that began, in 2011.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our current or any future products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. In international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. Glybera and our future products, if any, might not be considered medically reasonable and necessary for a specific indication or cost-effective by third-party payers. An adequate level of reimbursement might not be available for such products and third-party payers' reimbursement policies might adversely affect our or our collaborators' ability to sell Glybera and any future products profitably.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-approval testing and other requirements.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the U.S. or abroad. If we or our collaborators are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or our collaborators are not able to maintain regulatory compliance, our product candidates may lose any marketing approval that may have been obtained and we may not achieve or sustain profitability, which would adversely affect our business.

Foreign governments tend to impose strict price controls, which may adversely affect our future profitability.

In most foreign countries, particularly those in the EU, prescription drug pricing and/or reimbursement is subject to governmental control. In those countries that impose price controls, pricing negotiations with governmental authorities

can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies.



Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenue that are generated from the sale of the product in that country. If reimbursement of such products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, or if there is competition from lower priced cross-border sales, our profitability will be negatively affected.

#### Risks Related to Our Dependence on Third Parties

We depend on our collaborative relationship with Teva to further develop and commercialize TV-45070, and if our relationship is not successful or is terminated, we may not be able to effectively develop and/or commercialize TV-45070, which would have a material adverse effect on our business.

We depend on Teva to collaborate with us to develop and globally commercialize TV-45070. Under the agreement, Teva controls all decision-making with respect to the clinical development and commercialization for TV-45070.

As a result of our dependence on Teva, the eventual success or commercial viability of TV-45070 is largely beyond our control. The financial returns to us, if any, depend in large part on the achievement of development and commercialization milestones, plus a share of any revenue from sales. Therefore, our success, and any associated financial returns to us and our investors, will depend in large part on Teva's performance under the agreement. We are subject to a number of additional specific risks associated with our dependence on our collaborative relationship with Teva, including:

- adverse decisions by Teva or the Joint Development Committee regarding the development and commercialization of TV-45070;
- possible disagreements as to the timing, nature and extent of our development plans, including clinical trials or regulatory approval strategy;
- loss of significant rights if we fail to meet our obligations under the agreement;
- our limited control over clinical trials of TV-45070;
- changes in key management personnel at Teva, including in members of the Joint Development Committee; and
- possible disagreements with Teva regarding the agreement, for example, with regard to ownership of intellectual property rights.

If either we or Teva fail to perform our respective obligations, any clinical trial, regulatory approval or development progress could be significantly delayed or halted, could result in costly or time-consuming litigation or arbitration and could have a material adverse effect on our business.

Decisions by Teva to emphasize other drug candidates currently in its portfolio ahead of our product candidates, or to add competitive agents to its portfolio could result in a decision to terminate the agreement, in which event, among other things, we may be responsible for paying any remaining costs of all ongoing or future clinical trials.

In addition, Teva's executive offices and a substantial percentage of their manufacturing capabilities are located in Israel. Teva's Israeli operations are dependent upon materials imported from outside Israel, and Teva also exports significant amounts of products from Israel. Accordingly, our collaboration with Teva could be materially and adversely affected by acts of terrorism or if major hostilities were to occur in the Middle East or trade between Israel and its present trading partners were curtailed, including as a result of acts of terrorism in the U.S. or elsewhere.

Any of the above discussed scenarios could adversely affect the timing and extent of our development and commercialization activities, which could cause significant delays and funding shortfalls for those activities and seriously harm our business.

Our prospects for successful development and commercialization of our partnered products and product candidates are dependent upon the research, development and marketing efforts of our collaborators.

We have no control over the resources, time and effort that our collaborators may devote to our programs and limited access to information regarding or resulting from such programs. We are dependent on uniQure, and its licensee Chiesi to successfully commercialize Glybera and on Teva, Genentech, and Merck to fund and conduct the research and any clinical development of product candidates under our collaboration with each of them, and for the successful regulatory approval, marketing and commercialization of one or more of such products or product candidates. Such success will be subject to significant uncertainty.

Our ability to recognize revenue from successful collaborations may be impaired by multiple factors including:

- a collaborator may shift its priorities and resources away from our programs due to a change in business strategies, or a merger, acquisition, sale or downsizing of its company or business unit;
- a collaborator may cease development in therapeutic areas which are the subject of our strategic alliances;
- a collaborator may change the success criteria for a particular program or product candidate thereby delaying or ceasing development of such program or candidate;
  - a significant delay in initiation of certain development activities by a collaborator will also delay payment of milestones tied to such activities, thereby impacting our ability to fund our own activities;
- a collaborator could develop a product that competes, either directly or indirectly, with our current or future products, if any;
  - a collaborator with commercialization obligations may not commit sufficient financial or human resources to the marketing, distribution or sale of a product;
- a collaborator with manufacturing responsibilities may encounter regulatory, resource or quality issues and be unable to meet demand requirements;
- a collaborator may exercise its rights under the agreement to terminate our collaboration;
- a dispute may arise between us and a collaborator concerning the research or development of a product candidate, commercialization of a product or payment of royalties or milestone payments, any of which could result in a delay in milestones, royalty payments or termination of a program and possibly resulting in costly litigation or arbitration which may divert management attention and resources;
- a collaborator may not adequately protect the intellectual property rights associated with a product or product candidate; and
- a collaborator may use our proprietary information or intellectual property in such a way as to invite litigation from a third party.

If our collaborators do not perform in the manner we expect or fulfill their responsibilities in a timely manner, or at all, the clinical development, regulatory approval and commercialization efforts could be delayed, terminated or be commercially unsuccessful. Conflicts between us and our collaborators may arise. In the event of termination of one or more of our collaboration agreements, it may become necessary for us to assume the responsibility of any terminated product or product candidates at our own expense or seek new collaborators. In that event, we would likely be required to limit the size and scope of one or more of our independent programs or increase our expenditures and seek additional funding which may not be available on acceptable terms or at all, and our business would be materially and adversely affected.

We may not be successful in establishing new collaborations or maintaining our existing alliances, which could adversely affect our ability to develop future product candidates and commercialize future products.

We may seek to enter into additional product collaborations in the future, including alliances with other biotechnology or pharmaceutical companies, to enhance and accelerate the development of our future product candidates and the commercialization of any resulting products. We face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish other collaborations or other alternative arrangements for any future product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaboration effort and/or third parties may view our product candidates as lacking the requisite potential to demonstrate safety and efficacy. Even if we are successful in our efforts to establish collaborations, the terms that we agree upon may not be favorable to us and we may not be able to maintain such collaborations if, for example, development or approval of a product candidate is delayed or sales of an approved product are disappointing.

If any of our existing collaboration agreements is terminated, or if we determine that entering into other product collaborations is in our best interest but we either fail to enter into, delay in entering into or fail to maintain such collaborations:

- the development of certain of our current or future product candidates may be terminated or delayed;
- our cash expenditures related to development of our product candidates would increase significantly and we may need to seek additional financing sooner than expected;
- we may be required to hire additional employees or otherwise develop expertise, such as clinical, regulatory, sales and marketing expertise, which we do not currently have;
- we will bear all of the risk related to the development of any such product candidates; and
- the competitiveness of any product that is commercialized could be reduced.

We intend to rely on third-party manufacturers to produce our clinical product candidate supplies. Any failure by a third-party manufacturer to produce acceptable supplies for us may delay or impair our ability to initiate or complete our clinical trials or commercialize approved products.

We do not currently own or operate any manufacturing facilities nor do we have any in-house manufacturing experience or personnel. We rely on our collaborators to manufacture product candidates licensed to them or work with multiple third party contract manufacturers to produce sufficient quantities of materials required for the manufacture of our product candidates for preclinical testing and clinical trials and intend to do so for the commercial manufacture of our products. If we are unable to arrange for such third-party manufacturing sources, or fail to do so on commercially reasonable terms, we may not be able to successfully produce sufficient supply of product candidate or we may be delayed in doing so. Such failure or substantial delay could materially harm our business.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including reliance on the third party for regulatory compliance and quality control and assurance, volume production, the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control (including a failure to synthesize and manufacture our product candidates in accordance with our product specifications) and the possibility of termination or nonrenewal of the agreement by the third party at a time that is costly or damaging to us. In addition, the FDA, EMA and other regulatory authorities require that our product candidates be manufactured according to cGMP and similar foreign standards. Pharmaceutical manufacturers and their subcontractors are required to register their facilities and/or products manufactured at the time of submission of the marketing application and then annually thereafter with the FDA and certain state and foreign agencies. They are also subject to periodic unannounced inspections by the FDA, state and other foreign authorities. Any subsequent discovery of problems with a product, or a manufacturing or laboratory facility used by us or our collaborators, may

result in restrictions on the product or on the manufacturing or laboratory facility, including marketed product recall, suspension of manufacturing, product seizure, or a voluntary withdrawal of the drug from the market. Any failure by our third-party manufacturers to comply with cGMP or failure to scale up manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner, could lead to a delay in, or failure to obtain, regulatory approval of any of our product candidates.

We rely on third parties to monitor, support, conduct and/or oversee clinical trials of the product candidates that we are developing independently and, in some cases, to maintain regulatory files for those product candidates. We may not be able to obtain regulatory approval for our product candidates or commercialize any products that may result from our development efforts, if we are not able to maintain or secure agreements with such third parties on acceptable terms, if these third parties do not perform their services as required, or if these third parties fail to timely transfer any regulatory information held by them to us.

We rely on entities outside of our control, which may include academic institutions, CROs, hospitals, clinics and other third-party collaborators, to monitor, support, conduct and/or oversee preclinical and clinical studies of our current and future product candidates. We also rely on third parties to perform clinical trials on our current and future product candidates when they reach that stage. As a result, we have less control over the timing and cost of these studies and the ability to recruit trial subjects than if we conducted these trials with our own personnel.

If we are unable to maintain or enter into agreements with these third parties on acceptable terms, or if any such engagement is terminated prematurely, we may be unable to enroll patients on a timely basis or otherwise conduct our trials in the manner we anticipate. In addition, there is no guarantee that these third parties will devote adequate time and resources to our studies or perform as required by our contract or in accordance with regulatory requirements, including maintenance of clinical trial information regarding our product candidates. If these third parties fail to meet expected deadlines, fail to transfer to us any regulatory information in a timely manner, fail to adhere to protocols or fail to act in accordance with regulatory requirements or our agreements with them, or if they otherwise perform in a substandard manner or in a way that compromises the quality or accuracy of their activities or the data they obtain, then clinical trials of our future product candidates may be extended or delayed with additional costs incurred, or our data may be rejected by the FDA, EMA or other regulatory agencies.

Ultimately, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with cGCP regulations and guidelines enforced by the FDA, the competent authorities of the member states of the European Economic Area and comparable foreign regulatory authorities for products in clinical development. Regulatory authorities enforce these cGCP regulations through periodic inspections of clinical trial sponsors, principal investigators and clinical trial sites. If we or any of our CROs fail to comply with applicable cGCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and our submission of marketing applications may be delayed or the FDA may require us to perform additional clinical trials before approving our marketing applications. Upon inspection, the FDA could determine that any of our clinical trials fail or have failed to comply with applicable cGCP regulations. In addition, our clinical trials must be conducted with product produced under the cGMP regulations enforced by the FDA, and our clinical trials may require a large number of test subjects. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and increase our costs. Moreover, our business may be implicated if any of our CROs violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

If any of our clinical trial sites terminates for any reason, we may experience the loss of follow-up information on patients enrolled in our ongoing clinical trials unless we are able to transfer the care of those patients to another qualified clinical trial site. Further, if our relationship with any of our CROs is terminated, we may be unable to enter into arrangements with alternative CROs on commercially reasonable terms, or at all.

Switching or adding CROs or other suppliers can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO or supplier commences work. As a result,

delays may occur, which can materially impact our ability to meet our desired clinical development timelines. If we are required to seek alternative supply arrangements, the resulting delays and potential inability to find a suitable replacement could materially and adversely impact our business.

## Risks Related to Intellectual Property

We could be unsuccessful in obtaining or maintaining adequate patent protection for one or more of our products or product candidates.

Our commercial success will depend, in large part, on our ability to obtain and maintain patent and other intellectual property protection with respect to our product candidates. Patents might not be issued or granted with respect to our patent applications that are currently pending, and issued or granted patents might later be found to be invalid or unenforceable, be interpreted in a manner that does not adequately protect our current product or any future products, or fail to otherwise provide us with any competitive advantage. The patent position of biotechnology and pharmaceutical companies is generally uncertain because it involves complex legal and factual considerations. The standards applied by the U.S. Patent and Trademark Office, or USPTO, and foreign patent offices in granting patents are not always applied uniformly or predictably. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in biotechnology and pharmaceutical patents. Consequently, patents may not issue from our pending patent applications. As such, we do not know the degree of future protection that we will have on our proprietary products and technology, if any, and a failure to obtain adequate intellectual property protection with respect to our product candidates and proprietary technology could have a material adverse impact on our business.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to be paid to the USPTO and various governmental patent agencies outside of the U.S. in several stages over the lifetime of the patents and/or applications. We employ reputable law firms and other professionals and rely on such third parties to effect payment of these fees with respect to the patents and patent applications that we own, and we rely upon our licensors or our other collaborators to effect payment of these fees with respect to the patents and patent applications that we license. The USPTO and various non-US governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply with respect to the patents and patent applications that we own, and we rely upon our licensors or our other collaborators to effect compliance with respect to the patents and patent applications that we license. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Our intellectual property rights will not necessarily provide us with competitive advantages.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage.

The following examples are illustrative:

- others may be able to make compounds that are similar to our product candidates but that are not covered by the claims of the patents that we or our collaborators own or have exclusively licensed;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;



- we may obtain patents for certain compounds many years before we obtain marketing approval for products containing such compounds, and because patents have a limited life, which may begin to run prior to the commercial sale of the related product, the commercial value of our patents may be limited;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may fail to develop additional proprietary technologies that are patentable;
- the laws of certain foreign countries may not protect our intellectual property rights to the same extent as the laws of the U.S., or we may fail to apply for or obtain adequate intellectual property protection in all the jurisdictions in which we operate; and
- the patents of others may have an adverse effect on our business, for example by preventing us from marketing one or more of our product candidates for one or more indications.

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Any of the aforementioned threats to our competitive advantage could have a material adverse effect on our business.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the U.S. can be less extensive than those in the U.S. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the U.S. These products may compete with our current or future products, if any, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Our patents covering one or more of our products or product candidates could be found invalid or unenforceable if challenged.

Any of our intellectual property rights could be challenged or invalidated despite measures we take to obtain patent and other intellectual property protection with respect to our product candidates and proprietary technology. For example, if we were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the U.S. and in some other jurisdictions, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld material information from the USPTO or the applicable foreign counterpart, or made a misleading statement, during prosecution. A litigant or the USPTO itself could challenge our patents on this basis even if we believe that we have conducted our patent prosecution in accordance with the duty of candor and in good faith. The outcome following such a challenge is unpredictable.

With respect to challenges to the validity of our patents, for example, there might be invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on a product candidate. Even if a defendant does not prevail on a legal assertion of invalidity and/or unenforceability, our patent claims may be construed in a manner that would limit our ability to enforce such claims against the defendant and others. The cost of defending such a challenge, particularly in a foreign jurisdiction, and any resulting loss of patent

protection could have a material adverse impact on one or more of our product candidates and our business.

Enforcing our intellectual property rights against third parties may also cause such third parties to file other counterclaims against us, which could be costly to defend, particularly in a foreign jurisdiction, and could require us to pay substantial damages, cease the sale of certain products or enter into a license agreement and pay royalties (which may not be possible on commercially reasonable terms or at all). Any efforts to enforce our intellectual property rights are also likely to be costly and may divert the efforts of our scientific and management personnel.

Patent protection and patent prosecution for some of our product candidates is dependent on, and the ability to assert patents and defend them against claims of invalidity is maintained by, third parties.

There have been and may be times in the future when certain patents that relate to our product candidates or any approved products are controlled by our licensees or licensors. Although we may, under such arrangements, have rights to consult with our collaborators on actions taken as well as back-up rights of prosecution and enforcement, we have in the past and may in the future relinquish rights to prosecute and maintain patents and patent applications within our portfolio as well as the ability to assert such patents against infringers. Currently, some of these rights relating to the patent portfolios for Glybera, TV-45070, GDC-0276 and GDC-0310, and some of our earlier stage product candidates are held by our collaborators.

If any current or future licensee or licensor with rights to prosecute, assert or defend patents related to our product candidates fails to appropriately prosecute and maintain patent protection for patents covering any of our product candidates, or if patents covering any of our product candidates are asserted against infringers or defended against claims of invalidity or unenforceability in a manner which adversely affects such coverage, our ability to develop and commercialize any such product candidate may be adversely affected and we may not be able to prevent competitors from making, using and selling competing products.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or one of our licensors is not valid or is unenforceable, or may refuse to stop the other party in such infringement proceeding from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly, and could put any of our patent applications at risk of not yielding an issued patent.

Interference proceedings, derivation proceedings, entitlement proceedings, ex parte reexamination, inter partes reexamination, inter partes review, post-grant review, and opposition proceedings provoked by third parties or brought by the USPTO or any foreign patent authority may be used to challenge inventorship, ownership, claim scope, or validity of our patent applications. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms, if any license is offered at all. Litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees.

We may not be able to prevent, alone or with our licensors, misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the U.S. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares.

Claims that our product candidates or the sale or use of our future products infringe the patent or other intellectual property rights of third parties could result in costly litigation or could require substantial time and money to resolve, even if litigation is avoided.

Our commercial success depends upon our ability to develop product candidates and commercialize products that may be approved in the future, using our proprietary technology without infringing the intellectual property rights of others. Our product or product candidates or any uses of them may now and in the future infringe third-party patents or other intellectual property rights. Third parties might allege that we or our collaborators are infringing their patent rights or that we have misappropriated their trade secrets, or that we are otherwise violating their intellectual property rights, whether with respect to the manner in which we have conducted our research or to the composition, use or manufacture of the compounds we have developed or are developing with our collaborators. Such third parties might resort to litigation against us or other parties we have agreed to indemnify, which litigation could be based on either existing intellectual property or intellectual property that arises in the future.

It is possible that relevant patents or patent applications held by third parties will cover our product candidates at the time of launch and we may also fail to identify, relevant patents or patent applications held by third parties that cover our product candidates. For example, applications filed before November 29, 2000, and certain applications filed after that date that will not be filed outside the U.S. remain confidential until patents issue. Other patent applications in the U.S. and several other jurisdictions are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Furthermore, publication of discoveries in the scientific or patent literature often lags behind actual discoveries. Therefore, we cannot be certain that we or our collaborators were the first to invent, or the first to file patent applications on, our product candidates or for their uses, or that our product candidates will not infringe patents that are currently issued or that are issued in the future. In the event that a third party has also filed a patent application covering one of our product candidates or a similar invention, we may have to participate in an adversarial proceeding, known as an interference, declared by the USPTO or its foreign counterpart to determine priority of invention. Additionally, pending patent applications and patents which have been published can, subject to certain limitations, be later amended in a manner that could cover our current or future products, if any, or their use.

Defending against claims of patent infringement, misappropriation of trade secrets or other violations of intellectual property rights could be costly and time consuming, regardless of the outcome. Thus, even if we were to ultimately prevail, or to settle at an early stage, such litigation could burden us with substantial unanticipated costs. In addition, litigation or threatened litigation could result in significant demands on the time and attention of our management team, distracting them from the pursuit of other company business. Claims that our product candidates or the sale or use of our future products infringe, misappropriate or otherwise violate third-party intellectual property rights could therefore have a material adverse impact on our business.

Most of our competitors are larger than we are and have substantially greater financial resources. They are, therefore, likely to be able to sustain the costs of complex intellectual property litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to conduct our clinical trials, continue our internal research programs, in-license needed technology, or enter into strategic collaborations that would help us bring our product candidates to market.

In addition, any future intellectual property litigation, interference or other administrative proceedings will result in additional expense and distraction of our personnel. An adverse outcome in such litigation or proceedings may expose us or any future strategic collaborators to loss of our proprietary position, expose us to significant liabilities, or require us to seek licenses that may not be available on commercially acceptable terms, if at all, each of which could have a material adverse effect on our business.

Unfavorable outcomes in intellectual property litigation could limit our research and development activities and/or our ability to commercialize certain products.

If third parties successfully assert their intellectual property rights against us, we might be barred from using certain aspects of our technology, or barred from developing and commercializing certain products. Prohibitions against using certain technologies, or prohibitions against commercializing certain products, could be imposed by a court or by a settlement agreement between us and a plaintiff. In addition, if we are unsuccessful in defending against allegations that we have infringed, misappropriated or otherwise violated patent or other intellectual property rights of others, we may be forced to pay substantial damage awards to the plaintiff. There is inevitable uncertainty in intellectual property litigation and we could lose, even if the case against us is weak or flawed. If litigation leads to an outcome unfavorable to us, we may be required to obtain a license from the intellectual property owner in order to continue our research and development programs or to market any resulting product. It is possible that the necessary license will not be available to us on commercially acceptable terms, or at all. Alternatively, we may be required to modify or redesign our current or future products, if any, in order to avoid infringing or otherwise violating third-party

intellectual property rights. This may not be technically or commercially feasible, may render those products less competitive, or may delay or prevent the entry of those products to the market. Any of the foregoing could limit our research and development activities, our ability to commercialize one or more product candidates, or both.

In order to avoid or settle potential claims with respect to any patent or other intellectual property rights of third parties, we may choose or be required to seek a license from a third party and be required to pay license fees or royalties or both, which could be substantial. These licenses may not be available on acceptable terms, or at all. Even if we or any future collaborators were able to obtain a license, the rights may be nonexclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced, by court order or otherwise, to cease some or all aspects of our business operations, if, as a result of actual or threatened patent or other intellectual property claims, we are unable to enter into licenses on acceptable terms. Further, we could be found liable for significant monetary damages as a result of claims of intellectual property infringement. For example, we have received, and may in the future receive, offers to license and demands to license from third parties claiming that we are infringing their intellectual property or owe license fees and, even if such claims are without merit, we could fail to successfully avoid or settle such claims.

If Teva, uniQure, Genentech or Merck license or otherwise acquire rights to intellectual property controlled by a third party in various circumstances, for example, where a product could not be legally developed or commercialized in a country without the third-party intellectual property right or, where it is decided that it would be useful to acquire such third-party right to develop or commercialize the product, they are eligible under our collaboration agreements to decrease payments payable to us on a product-by-product basis and, in certain cases, on a country-by-country basis. Any of the foregoing events could harm our business significantly.

If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties, we could lose license rights that are important to our business.

The patent portfolio for Glybera is in-licensed from UBC. Under our existing license agreements, we are subject to various obligations, including diligence obligations such as development and commercialization obligations, as well as potential royalty payments and other obligations. If we fail to comply with any of these obligations or otherwise breach our license agreements, our licensing partners may have the right to terminate the applicable license in whole or in part. Generally, the loss of any one of our current licenses, or any other license we may acquire in the future, could materially harm our business, prospects, financial condition and results of operations.

Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of trade secrets and other proprietary information, which would harm our competitive position.

In addition to patents, we rely on trade secrets, technical know-how and proprietary information concerning our Extreme Genetics discovery platform, business strategy and product candidates in order to protect our competitive position, which are difficult to protect. In the course of our research and development activities and our business activities, we often rely on confidentiality agreements to protect our proprietary information. Such confidentiality agreements are used, for example, when we talk to vendors of laboratory or clinical development services or potential strategic collaborators. In addition, each of our employees and consultants is required to sign a confidentiality agreement and invention assignment agreement upon joining our company. Our employees, consultants, contractors, business partners or outside scientific collaborators might intentionally or inadvertently disclose our trade secret information in breach of these confidentiality agreements or our trade secrets may otherwise be misappropriated. Our collaborators might also have rights to publish data and we might fail to apply for patent protection prior to such publication. It is possible that a competitor will make use of such information, and that our competitive position will be compromised. In addition, to the extent that our employees, consultants or contractors use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. Enforcing a claim that a third party illegally obtained and is using any of our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the U.S. sometimes are less willing than U.S. courts to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. If we cannot maintain the confidentiality of our proprietary technology and other confidential information, then our ability to obtain patent protection or to protect our trade secret information would be jeopardized, which would adversely affect our competitive position.

Patent reform legislation and recent court decisions could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The USPTO has and continues to develop and implement regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act. The full effect of these changes are currently unclear as the USPTO has not yet adopted all pertinent final rules and regulations, the courts have yet to address these



provisions and the applicability of the Leahy-Smith Act and new regulations on specific patents, including our patents discussed herein, have not been determined and would need to be reviewed. Accordingly, it is not yet clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. As a result, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents, all of which could have a material adverse effect on our business and financial condition. On June 13, 2013, the U.S. Supreme Court decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, held that isolated DNA sequences are not patentable. In December 2014, the USPTO issued its Interim Guidance on Patent Subject Matter Eligibility, in which it extended Myriad's "marked difference" standard for patent subject matter eligibility to all potential natural products. This standard applies to patent claims that recite not only nucleic acids (such as DNA in Myriad), but also other subject matter that could be considered a natural product, such as peptides, proteins, extracts, organisms, antibodies, chemicals, and minerals. As a consequence of the Myriad decision and the USPTO's Interim Guidance, if any of our future product candidates utilize isolated DNA, peptides, proteins or the like, we will not be able to obtain patents in the U.S. claiming such novel gene targets that we discover, which could limit our ability to prevent third parties from developing drugs directed against such targets.

If we do not obtain protection under the Hatch-Waxman Act and similar legislation outside of the U.S. by extending the patent terms for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, if any, one or more U.S. patents may be eligible for limited patent term restoration under the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during clinical testing of the product and the subsequent FDA regulatory review process. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request.

If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially.

We have not registered our corporate name as a trademark in all of our potential markets, and failure to secure those registrations could adversely affect our business.

Our corporate name, Xenon, has not been trademarked in each market where we operate and plan to operate. Our trademark applications for our corporate name or the name of our products may not be allowed for registration, and our registered trademarks may not be maintained or enforced. During trademark registration proceedings, we may receive rejections, which we may be unable to overcome in our responses. Third parties may also attempt to register trademarks utilizing the Xenon name on their products, and we may not be successful in preventing such usage. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would.

Intellectual property litigation may lead to unfavorable publicity that harms our reputation and causes the market price of our common shares to decline.

During the course of any intellectual property litigation, there could be public announcements of the initiation of the litigation as well as results of hearings, rulings on motions, and other interim proceedings in the litigation. If securities analysts or investors regard these announcements as negative, the perceived value of our existing products, programs or intellectual property could be diminished. Accordingly, the market price of our common shares may decline. Such announcements could also harm our reputation or the market for our future products, which could have a material adverse effect on our business.

#### Risks Related to Our Industry

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our current and any future products.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates, and we will face an even greater risk if we commercialize any product candidates. For example, we may be sued if any of our product candidates, including any that are developed in combination therapies, allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims

may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. There is also risk that third parties we have agreed to indemnify could incur liability. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates or any resulting products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;

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- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- the inability to commercialize our product candidates; and
- a decline in our share price.

We currently carry product liability insurance of \$5,000,000 per occurrence and \$5,000,000 aggregate limit. We believe our product liability insurance coverage is appropriate in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may then be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our common share price to decline and, if judgments exceed our insurance coverage, could adversely affect our future results of operations and business.

Patients with the diseases targeted by our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life-threatening conditions. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market those product candidates, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

Our current and future relationships with customers and third-party payers in the U.S. and elsewhere will be subject, directly or indirectly, to applicable federal and state anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security, and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens, and diminished profits and future earnings.

Healthcare providers, physicians and third-party payers in the U.S. and elsewhere play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payers and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, that may constrain the business or financial arrangements and relationships through which we market, sell and distribute any products for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by the federal government and by the U.S. states and foreign jurisdictions in which we conduct our business. The applicable federal, state and foreign healthcare laws and regulations that may affect our ability to operate include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, which impose criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or

entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, or other third party payers claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

·HIPAA, which imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;

·HIPAA, as amended by HITECH, and their respective implementing regulations, which impose obligations on covered healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that create, receive, maintain, or transmit individually identifiable health information for or on their behalf, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

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- the federal Open Payments program; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the collection, export, privacy, use and security of biological materials and health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, including, without limitation, damages, fines, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations, which could have a material adverse effect on our business. If any of the physicians or other providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which could also materially affect our business.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

Our research and development activities involve the controlled use of potentially harmful biological materials as well as hazardous materials, chemicals, and various radioactive compounds typically employed in molecular and cellular biology. For example, we routinely use cells in culture and we employ small amounts of radioisotopes. We cannot completely eliminate the risk of accidental contamination or injury from the use, storage, handling, or disposal of these materials through our maintenance of up-to-date licensing and training programs. In the event of contamination or injury, we could be held liable for damages that result, and any liability could exceed our resources. We currently carry insurance covering certain claims arising from our use of these materials. However, if we are unable to maintain our insurance coverage at a reasonable cost and with adequate coverage, our insurance may not cover any liability that may arise. We are subject to U.S. and Canadian federal, provincial, and local laws and regulations governing the use, storage, handling, and disposal of these materials and specified waste products. Complying with regulations regarding the use of these materials could be costly, and if we fail to comply with these regulations, it could have a material adverse effect on our operations and profitability.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from serious disaster.

Our headquarters are located in Burnaby, British Columbia, Canada. We are vulnerable to natural disasters such as earthquakes that could disrupt our operations. If a natural disaster, power outage, fire or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. We do not carry insurance for earthquakes or other natural disasters and although our business interruption insurance applies in the event of an earthquake, we may not carry sufficient business interruption insurance to compensate us for all losses

that may occur. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business. In addition, we may lose samples or other valuable data. The occurrence of any of the forgoing could have a material adverse effect on our business.

## Risks Related to Our Common Shares

Our share price may be volatile, and purchasers of our common shares could incur substantial losses.

Our share price has fluctuated in the past and is likely to be volatile in the future. As a result of this volatility, investors may experience losses on their investment in our common shares. The market price for our common shares may be influenced by many factors, including the following:

- actions by any of our collaborators regarding our product candidates they are developing, including announcements regarding clinical or regulatory decisions or developments or our collaboration;
- announcements by us or our competitors of new products, product candidates or new uses for existing products, significant contracts, commercial relationships or capital commitments and the timing of these introductions or announcements;
- unanticipated serious safety concerns related to Glybera or to the use of any of our products and product candidates;
- results from or delays of clinical trials of our product candidates;
- failure to obtain or delays in obtaining or maintaining product approvals or clearances from regulatory authorities;
- adverse regulatory or reimbursement announcements;
- announcements by us or our competitors of significant acquisitions, strategic collaborations, joint ventures or capital commitments;
- the results of our efforts to discover or develop additional product candidates;
- our dependence on third parties, including our collaborators, CROs, clinical trial sponsors and clinical investigators;
- regulatory or legal developments in Canada, the U.S. or other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key scientific or management personnel;
- our ability to successfully commercialize our future product candidates we develop independently, if approved;
- the level of expenses related to any of our product candidates or clinical development programs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- actual or anticipated quarterly variations in our financial results or those of our competitors;
- any change to the composition of the board of directors or key personnel;
- sales of common shares by us or our shareholders in the future, as well as the overall trading volume of our common shares;
- changes in the structure of healthcare payment systems;
- commencement of, or our involvement in, litigation;
- general economic, industry and market conditions in the pharmaceutical and biotechnology sectors and other factors that may be unrelated to our operating performance or the operating performance of our competitors, including changes in market valuations of similar companies; and
- the other factors described in this “Risk Factors” section.

In addition, the stock market in general, and NASDAQ and the biopharmaceutical industry in particular, have from time to time experienced volatility that often has been unrelated to the operating performance of the underlying companies. These broad market and industry fluctuations may adversely affect the market price of our common shares, regardless of our operating performance. In several recent situations where the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our shareholders were to bring a lawsuit against us, the defense and disposition of the lawsuit could be costly and divert the time and attention of our management and harm our operating results.



Future sales of our common shares in the public market could cause our share price to fall.

Our share price could decline as a result of sales of a large number of our common shares or the perception that these sales could occur. These sales, or the possibility that these sales may occur, also might make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

Certain holders of our common shares are party to our amended and restated investor rights agreement, as amended, and have rights, subject to some conditions, to require us to file registration statements covering the sale of their common shares or to include their common shares in registration statements that we may file for ourselves or other shareholders. We also register the offer and sale of all common shares that we may issue under our equity compensation plans.

In addition, in the future, we may issue additional common shares or other equity or debt securities convertible into common shares in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise. Any such issuance could result in substantial dilution to our existing shareholders and could cause our common share price to decline.

Provisions in our corporate charter documents and Canadian law could make an acquisition of us, which may be beneficial to our shareholders, more difficult and may prevent attempts by our shareholders to replace or remove our current management and/or limit the market price of our common shares.

Provisions in our articles and our by-laws, as well as certain provisions under the Canada Business Corporations Act, or CBCA, and applicable Canadian securities laws, may discourage, delay or prevent a merger, acquisition or other change in control of us that shareholders may consider favorable, including transactions in which they might otherwise receive a premium for their common shares. These provisions could also limit the price that investors might be willing to pay in the future for our common shares, thereby depressing the market price of our common shares. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our shareholders to replace or remove our current management by making it more difficult for shareholders to replace members of our board of directors. Among other things, these provisions include the following:

- shareholders cannot amend our articles unless such amendment is approved by shareholders holding at least two-thirds of the shares entitled to vote on such approval;
- our board of directors may, without shareholder approval, issue preferred shares having any terms, conditions, rights, preferences and privileges as the board of directors may determine; and
- shareholders must give advance notice to nominate directors or to submit proposals for consideration at shareholders' meetings.

Any provision in our articles, by-laws, under the CBCA or under any applicable Canadian securities law that has the effect of delaying or deterring a change in control could limit the opportunity for our shareholders to receive a premium for their common shares, and could also affect the price that some investors are willing to pay for our common shares.

U.S. civil liabilities may not be enforceable against us, our directors, or our officers

We are governed by the CBCA and our principal place of business is in Canada. Many of our directors and officers reside outside of the U.S., and all or a substantial portion of their assets as well as all or a substantial portion of our assets are located outside the U.S. As a result, it may be difficult for investors to effect service of process within the U.S. upon us and such directors and officers or to enforce judgments obtained against us or such persons, in U.S. courts, in any action, including actions predicated upon the civil liability provisions of U.S. federal securities laws or

any other laws of the U.S. Additionally, rights predicated solely upon civil liability provisions of U.S. federal securities laws or any other laws of the U.S. may not be enforceable in original actions, or actions to enforce judgments obtained in U.S. courts, brought in Canadian courts, including courts in the Province of British Columbia.

We are governed by the corporate laws of Canada which in some cases have a different effect on shareholders than the corporate laws of Delaware, U.S.

We are governed by the CBCA and other relevant laws, which may affect the rights of shareholders differently than those of a company governed by the laws of a U.S. jurisdiction, and may, together with our charter documents, have the effect of delaying, deferring or discouraging another party from acquiring control of our company by means of a tender offer, a proxy contest or otherwise, or may affect the price an acquiring party would be willing to offer in such an instance. The material differences between the CBCA and Delaware General Corporation Law, or DGCL, that may have the greatest such effect include, but are not limited to, the following: (i) for material corporate transactions (such as mergers and amalgamations, other extraordinary corporate transactions or amendments to our articles) the CBCA generally requires a two-thirds majority vote by shareholders, whereas DGCL generally only requires a majority vote; and (ii) under the CBCA a holder of 5% or more of our common shares can requisition a special meeting of shareholders, whereas such right does not exist under the DGCL.

An active trading market for our common shares may not be maintained.

Our common shares are currently traded on NASDAQ, but we can provide no assurance that we will be able to maintain an active trading market on NASDAQ or any other exchange in the future. If an active market for our common shares is not maintained, it may be difficult for our shareholders to sell the common shares they have purchased without depressing the market price for the shares or at all. Further, an inactive market may also impair our ability to raise capital by selling additional common shares and may impair our ability to enter into strategic collaborations or acquire companies or products by using our common shares as consideration.

Complying with the laws and regulations affecting public companies will increase our costs and the demands on management and could harm our operating results and our ability to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common shares.

As a public company, and particularly after we cease to be an “emerging growth company,” we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and the related rules and regulations subsequently implemented by the Securities and Exchange Commission, or SEC, the applicable Canadian securities regulators and NASDAQ impose numerous requirements on public companies, including requiring changes in corporate governance practices. Also, the Securities Exchange Act of 1934, as amended, or the Exchange Act, requires, among other things, that we file annual, quarterly and current reports with respect to our business and operating results. We anticipate that we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge to address the added burdens of operating as a public company. Our management and other personnel have and will continue to devote a substantial amount of time to compliance with these laws and regulations. These requirements have increased and will continue to increase our legal, accounting, and financial compliance costs and have made and will continue to make some activities more time-consuming and costly. For example, these rules and regulations make it difficult and expensive for us to maintain director and officer liability insurance and we may be required to accept reduced policy limits and coverage or to incur substantial costs to maintain the same or similar coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or our board committees or as executive officers.

The Sarbanes-Oxley Act requires, among other things, that we assess the effectiveness of our internal control over financial reporting annually and the effectiveness of our disclosure controls and procedures quarterly. In particular, commencing with our second Annual Report on Form 10-K, Section 404 of the Sarbanes-Oxley Act, or Section 404, will require us to perform system and process evaluation and testing of our internal control over financial reporting to

allow management to report on, and our independent registered public accounting firm potentially to attest to, the effectiveness of our internal control over financial reporting. As an “emerging growth company” we expect to avail ourselves of the exemption from the requirement that our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting under Section 404. However, we may no longer avail ourselves of this exemption when we cease to be an “emerging growth company.” When our independent registered public accounting firm is required to undertake an assessment of our internal control over financial reporting, the cost of our compliance with Section 404 will correspondingly increase. Our compliance with applicable provisions of Section 404 will require that we incur substantial accounting expense and expend significant management time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements. Moreover, if we are not able to comply with the requirements of Section 404 applicable to us in a timely manner, or if we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our common shares could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources.

Furthermore, investor perceptions of our company may suffer if deficiencies are found, and this could cause a decline in the market price of our common shares. Irrespective of compliance with Section 404, any failure of our internal control over financial reporting could have a material adverse effect on our stated operating results and harm our reputation. If we are unable to implement these requirements effectively or efficiently, it could harm our operations, financial reporting, or financial results and could result in an adverse opinion on our internal controls from our independent registered public accounting firm.

We are an “emerging growth company,” and any decision on our part to comply only with certain reduced reporting and disclosure requirements applicable to emerging growth companies could make our common shares less attractive to investors.

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an “emerging growth company,” we may choose to take advantage of exemptions from various reporting requirements applicable to other public companies that are not “emerging growth companies,” including, but not limited to, not being required to have our independent registered public accounting firm audit our internal control over financial reporting under Section 404, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We could be an “emerging growth company” for up to five years following the completion of our initial public offering, although, if we have more than \$1.0 billion in annual revenue, if the market value of our common shares held by non-affiliates exceeds \$700 million as of June 30 of any year, or we issue more than \$1.0 billion of non-convertible debt over a three-year period before the end of that five-year period, we would cease to be an “emerging growth company” as of the following December 31. Investors could find our common shares less attractive if we choose to rely on these exemptions. If some investors find our common shares less attractive as a result of any choices to reduce future disclosure, there may be a less active trading market for our common shares and our share price may be more volatile.

As an “emerging growth company,” the JOBS Act allows us to delay adoption of new or revised accounting pronouncements applicable to public companies until such pronouncements are made applicable to private companies. However, we previously decided to “opt out” of such extended transition period, and as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of the JOBS Act provides that our decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common shares.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our common shares.

We will be required to disclose changes made in our internal controls and procedures on a quarterly basis and our management will be required to assess the effectiveness of these controls annually. However, for as long as we are an “emerging growth company” under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. An independent assessment of the effectiveness of our internal controls could detect problems that our management’s assessment might not. In addition, our management did not perform an evaluation of our internal control over financial reporting as of December 31, 2014 or December 31, 2013 and our independent registered public accounting firm did not perform an evaluation of our internal control over financial reporting during any period in accordance with the provisions of the Sarbanes-Oxley Act. Had we and our independent registered public accounting firm performed such an evaluation, control deficiencies may have been identified by management or our independent registered public accounting firm, and those control deficiencies could have also represented one or more material weaknesses. Undetected material weaknesses in our internal controls could lead to financial statement restatements and require us to incur the expense of remediation.

Future sales and issuances of our common shares or rights to purchase common shares, including pursuant to our equity incentive plans, could cause you to incur dilution and could cause our share price to fall.

As of December 31, 2015, options to purchase 1,721,472 of our common shares with a weighted-average exercise price of \$6.95 per common share were outstanding. The exercise of any of these options would result in dilution to current shareholders. Further, because we will need to raise additional capital to fund our clinical development programs, we may in the future sell substantial amounts of common shares or securities convertible into or exchangeable for common shares. Pursuant to our equity incentive plans, our compensation committee (or a subset thereof) is authorized to grant equity-based incentive awards to our employees, directors and consultants. Future option grants and issuances of common shares under our stock-based compensation plans may have an adverse effect on the market price of our common shares.

These future issuances of common shares or common share-related securities, together with the exercise of outstanding options and any additional common shares issued in connection with acquisitions, if any, may result in further dilution to our existing shareholders, and new investors could gain rights, preferences and privileges senior to those of holders of our common shares.

We are at risk of securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We do not anticipate paying any cash dividends on our common shares in the foreseeable future.

We do not currently intend to pay any cash dividends on our common shares in the foreseeable future. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common shares may be investors' sole source of gain for the foreseeable future.

NASDAQ may delist our securities from its exchange, which could limit investors' ability to make transactions in our securities and subject us to additional trading restrictions.

Our common shares are listed on NASDAQ under the trading symbol "XENE." Our securities may fail to meet the continued listing requirements to be listed on NASDAQ. If NASDAQ delists our common shares from trading on its exchange, we could face significant material adverse consequences, including:

- significant impairment of the liquidity for our common shares, which may substantially decrease the trading price of our common shares;
- a limited availability of market quotations for our securities;
- a determination that our common shares qualify as a "penny stock" which will require brokers trading in our common shares to adhere to more stringent rules and possibly resulting in a reduced level of trading activity in the secondary trading market for our common shares;
- a limited amount of news and analyst coverage for our company; and
- a decreased ability to issue additional securities or obtain additional financing in the future.

If securities or industry analysts do not publish research reports about our business, or if they issue an adverse opinion about our business, our share price and trading volume could decline.

The trading market for our common shares will be influenced by the research and reports that securities or industry analysts publish about us or our business. If too few securities or industry analysts cover our company, the trading price for our common shares would likely be negatively impacted. If securities and industry analysts who cover us downgrade our common shares or publish inaccurate or unfavorable research about our business, our share price would likely decline. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our common shares could decrease, which might cause our price and trading volume to decline.



Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our headquarters are located in Burnaby, British Columbia, where we occupy approximately 41,332 square feet of office and laboratory space. The term of the lease expires in March 2022. We currently pay an aggregate of approximately \$73,766 per month in base rent, property tax, common area maintenance fees and management fees, and the landlord holds a security deposit equal to approximately \$63,892. We believe that our existing facilities are adequate to meet our business requirements for the near-term and that additional space will be available on commercially reasonable terms, if required.

Item 3. Legal Proceedings

From time to time, we may become involved in legal proceedings or be subject to claims arising in the ordinary course of our business. We are not presently a party to any legal proceedings that, in the opinion of our management, would reasonably be expected to have a material adverse effect on our business, financial condition, operating results or cash flows if determined adversely to us. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures

Not applicable.

## PART II

## Item 5. Market for Registrant's Common Equity, Related Shareholder Matters and Issuer Purchases of Equity Securities

## Market Information

Our common shares have been traded on The NASDAQ Global Market since November 5, 2014 under the symbol "XENE." Prior to such time, there was no public market for our common shares. The following table sets forth the high and low sales prices per common share as reported on The NASDAQ Global Market for the periods indicated.

	High	Low
Year Ended December 31, 2016		
First Quarter (through March 4, 2016)	\$8.42	\$6.31
Year Ended December 31, 2015		
Fourth Quarter	\$10.07	\$7.25
Third Quarter	\$11.75	\$7.94
Second Quarter	\$17.50	\$11.43
First Quarter	\$23.50	\$14.03
Year Ended December 31, 2014		
Fourth Quarter (commencing November 5, 2014)	\$21.95	\$9.21

On March 4, 2016, the last reported sale price of our common share was \$7.22 per share.

## Holders

As of March 4, 2016, there were approximately 186 holders of record of our common shares. The actual number of shareholders is greater than this number of record holders and includes shareholders who are beneficial owners but whose shares are held in street name by brokers and other nominees.

## Dividends

We have never declared or paid any cash dividends on our common shares or any other securities. We currently anticipate that we will retain all available funds and any future earnings, if any, in the foreseeable future for use in the operation of our business and do not currently anticipate paying cash dividends in the foreseeable future. Payment of future cash dividends, if any, will be at the discretion of the board of directors, subject to applicable law and will depend on various factors, including our financial condition, operating results, current and anticipated cash needs, the requirements of current or then-existing debt instruments and other factors the board of directors deems relevant.

Canadian withholding tax at a rate of 25% (subject to reduction under the provisions of any applicable income tax treaty or convention to which Canada is a signatory) will be payable on the gross amount of dividends on our common shares paid or credited, or deemed to be paid or credited, to a holder of our common shares who, for purposes of the Income Tax Act (Canada), is not (and is not deemed to be) resident in Canada and who does not use or hold (and will not be deemed to use or hold) our common shares in, or in the course of, carrying on a business or part of a business in Canada, or a Non-Resident of Canada Holder. The Canadian withholding taxes will be deducted directly by us or our paying agent from the amount of the dividend otherwise payable and remitted to the Receiver General of Canada. The rate of withholding tax applicable to a dividend paid on our common shares to a Non-Resident of Canada Holder who is a resident of the U.S. for purposes of the Canada U.S. Tax Convention, or the Convention, beneficially owns the dividend and qualifies for the full benefits of the Convention will generally be reduced to 15% or, if such a

Non-Resident of Canada Holder is a corporation that owns (or, for purposes of the Convention, is considered to own) at least 10% of our voting shares, to 5%. Not all persons who are residents of the U.S. for purposes of the Convention will qualify for the benefits of the Convention. A Non-Resident of Canada Holder who is a resident of the U.S. is advised to consult his or her tax advisor in this regard. The rate of withholding tax on dividends is also reduced under other bilateral income tax treaties to which Canada is a signatory.

## Performance Graph

The following stock performance graph illustrates a comparison of the total cumulative shareholder return on our common shares from November 5, 2014, which is the date our common shares commenced trading on The NASDAQ Global Market, through December 31, 2015, to two indices: the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The graph assumes an initial investment of \$100 on November 5, 2014, and that any dividends were reinvested. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our common shares.

## Recent Sales of Unregistered Securities

On January 8, 2015 and February 3, 2015, we issued 5,144 and 5,144 common shares, respectively, that were not registered under the Securities Act of 1933, as amended, to Genworks Inc., a consultant, pursuant to the exercise of stock options for cash consideration with exercise proceeds of approximately CAD\$31,224 and CAD\$31,224, respectively.

The common shares issued pursuant to the exercise of options were offered, sold and issued pursuant to the Canadian prospectus exemption under section 2.42 of National Instrument 45-106—Prospectus and Registration Exemptions, or NI 45-106, as such securities were offered, sold and issued in accordance with the terms and conditions of securities that we had previously issued. The options described above were offered, sold and issued pursuant to the Canadian prospectus exemption under section 2.24 of NI 45-106 as such securities were offered, sold and issued by us to our directors, officers, employees and consultants.

This issuance of common shares upon exercise of stock options was exempt from registration under the Securities Act of 1933, as amended, under Section 4(a)(2) thereof as a transaction by an issuer not involving a public offering. The recipient acquired the securities for investment only and not with a view to or for sale in connection with any distribution of the securities and appropriate legends were affixed thereto.

## Issuer Repurchases of Equity Securities

None.

## Item 6. Selected Financial Data

The following selected financial data is derived from our audited financial statements and should be read in conjunction with, and is qualified in its entirety by, Item 7, “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” and Item 8, “Financial Statements and Supplementary Data” contained elsewhere in this Annual Report on Form 10-K. The selected Statements of Operations Data for the years ended December 31, 2015, 2014 and 2013 and Balance Sheet Data as of December 31, 2015 and 2014 have been derived from our audited financial statements appearing elsewhere in this Annual Report on Form 10-K. The selected Statements of Operations Data for the years ended December 31, 2012 and 2011 and Balance Sheet Data as of December 31, 2013, 2012 and 2011 have been derived from our audited financial statements that are not included in this Annual Report on Form 10-K. Historical results are not necessarily indicative of future results. Our audited annual financial statements have been prepared in U.S. dollars and in accordance with U.S. Generally Accepted Accounting Principles.

	Year Ended December 31,				
	2015	2014	2013	2012	2011
	(in thousands except per share amounts)				
<b>Statement of Operations Data:</b>					
<b>Revenue:</b>					
Collaboration revenue	\$15,573	\$28,366	\$27,352	\$14,300	\$6,915
Royalties	4	4	4	8	3
	15,577	28,370	27,356	14,308	6,918
<b>Operating expenses:</b>					
Research and development	15,152	11,768	12,303	10,455	12,302
General and administrative	9,786	5,496	5,341	7,006	6,730
Total operating expenses	24,938	17,264	17,644	17,461	19,032
Income (loss) from operations	(9,361 )	11,106	9,712	(3,153 )	(12,114)
<b>Other income (expense):</b>					
Interest income	542	568	338	144	153
Interest expense	—	—	(64 )	(93 )	(91 )
Foreign exchange gain (loss)	(6,933 )	1,344	2,035	(169 )	60
Gain (loss) on write-off and disposal of assets	—	—	11	(1,030 )	—
Net income (loss)	(15,752)	13,018	12,032	(4,301 )	(11,992)
Net income attributable to participating securities	—	—	8,199	—	—
Net income (loss) attributable to common shareholders	\$(15,752)	\$13,018	\$3,833	\$(4,301 )	\$(11,992)
Net income (loss) per share—basic <sup>(1)</sup>	\$(1.10 )	\$4.11	\$2.87	\$(3.24 )	\$(9.06 )
Net income (loss) per share—diluted <sup>(1)</sup>	\$(1.10 )	\$3.28	\$1.91	\$(3.24 )	\$(9.06 )
<b>Weighted-average common shares outstanding used</b>					
in computing basic net income (loss) per share <sup>(1)</sup>	14,282	3,166	1,338	1,327	1,324
<b>Weighted-average common shares outstanding used</b>					
in computing diluted net income (loss) per share <sup>(1)</sup>	14,282	3,964	2,009	1,327	1,324

(1) See Note 3(m) to our financial statements appearing elsewhere in this report for an explanation of the method used to calculate basic and diluted net income (loss) per common share and the weighted-average number of common shares used in computation of the per common share amounts.

As of December 31,

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	2015	2014	2013	2012	2011
	(in thousands)				
<b>Balance Sheet Data:</b>					
Cash, cash equivalents and marketable securities	\$58,651	\$84,041	\$49,276	\$60,162	\$14,924
Working capital	58,084	70,656	31,666	41,507	20,536
Total assets	63,949	87,418	54,487	63,305	30,465
Notes payable	—	—	—	1,665	1,586
Redeemable convertible preferred shares	—	—	102,488	102,488	102,488
Total shareholders' equity (deficit)	61,034	72,779	(78,372 )	(89,865 )	(86,316 )

## Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis together with Part II, Item 6 — “Selected Financial Data” and our financial statements and notes included elsewhere in this Annual Report. The following discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ from those expressed or implied in any forward-looking statements as a result of various factors, including those set forth under the caption Part I, Item 1A — “Risk Factors.” Throughout this discussion, unless the context specifies or implies otherwise, the terms “Xenon,” “we,” “us,” and “our” refer to Xenon Pharmaceuticals Inc.

### Overview

We are a clinical-stage biopharmaceutical company discovering and developing a pipeline of differentiated therapeutics for orphan indications that we intend to commercialize on our own, and for larger market indications that we intend to partner with global pharmaceutical companies. We have built a core enabling discovery platform for the discovery of validated drug targets by studying rare human diseases with extreme traits, including diseases caused by mutations in ion channels, known as channelopathies. We have an integrated platform that includes in-house capabilities for human genetics, small molecule drug discovery, as well as preclinical and clinical development.

Our pharmaceutical partners include Teva Pharmaceutical Industries, Ltd., or Teva (through its subsidiary, Ivax International GmbH), Genentech, Inc., or Genentech, and Merck & Co., Inc., or Merck (through its affiliate, Essex Chemie AG). Our pharmaceutical collaborations have generated in aggregate over \$155.0 million in non-equity funding to date with the potential to provide us with over \$1.0 billion in future milestone payments, as well as royalties and co-promotion income on product sales.

Our business was founded on our proprietary discovery platform, which we refer to as Extreme Genetics. Extreme Genetics involves the study of families where individuals exhibit inherited severe traits, or phenotypes. By identifying and characterizing single-gene defects responsible for these phenotypes, we gain insights into human disease biology to better select targets for therapeutic intervention. We believe that our Extreme Genetics discovery platform enhances the likelihood of discovering a drug target that has a major effect in humans. From these discoveries, we can gain an improved understanding of how a drug that modulates the target might act when given to a human.

Our Extreme Genetics discovery platform has yielded the first approved gene therapy product in the European Union, or the EU, and a broad proprietary development pipeline and multiple pharmaceutical partnerships, which include:

- Glybera, developed by our licensee uniQure Biopharma B.V., or uniQure, the first, and currently the only, gene therapy product approved in the EU for the treatment of the orphan disorder lipoprotein lipase deficiency, or LPLD. The first patient treated with Glybera as a commercially-available gene therapy was announced by uniQure in November 2015 and enabled by its commercialization partner in the EU, Chiesi Farmaceutici S.p.A., or Chiesi, which has sole control over commercialization in the EU;
- TV-45070 (formerly XEN402), a product candidate being developed in collaboration with Teva for the treatment of pain. Teva is currently conducting a randomized, double-blind, placebo-controlled Phase 2b clinical trial in patients with post-herpetic neuralgia, or PHN, with results expected in the second half of 2016. TV-45070 is a topically applied small-molecule inhibitor of the sodium channel Nav1.7 and other sodium channels, including those that are expressed in the pain-sensing peripheral nervous system;
- GDC-0276 and GDC-0310, which are both oral, selective Nav1.7 small-molecule inhibitors being developed in collaboration with Genentech for the potential treatment of pain. Phase 1 clinical trials for GDC-0276 and GDC-0310 are ongoing, and pending a full assessment of the results, Genentech intends to initiate a Phase 2 clinical trial in 2016. Xenon and Genentech also have an active research collaboration focused on other orally selective small molecule inhibitors of Nav1.7;

XEN801, a stearoyl Co-A desaturase-1, or SCD1, inhibitor being developed for the treatment of acne. SCD1 is an enzyme involved in lipid synthesis that is expressed in sebaceous glands in the skin. We have completed a Phase 1 clinical trial for XEN801 and initiated a Phase 2 clinical trial in February 2016 in patients with moderate to severe facial acne. We anticipate topline results in the fourth quarter of 2016; and

- additional proprietary preclinical programs including a Nav1.6 sodium channel inhibitor for the treatment of rare childhood epilepsy disorders, such as Dravet Syndrome, or DS, an orphan disease of severe childhood epilepsy. We expect to identify a development candidate in 2016 and file an investigational new drug, or IND, application for our Nav1.6 inhibitor in the first half of 2017.

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We have funded our operations through the sale of equity securities, funding received from our licensees and collaborators and, to a lesser extent, government funding. For 2015, 2014, and 2013, we recognized revenues of approximately \$15.6 million, \$28.4 million, and \$27.4 million, respectively, consisting primarily of funding from our collaborators. Though our revenue from our collaboration and license agreements resulted in net income of \$13.0 million for the year ended December 31, 2014 and \$12.0 million for the year ended December 31, 2013, we do not expect to have sustained profitability for the foreseeable future. We had net losses of \$15.8 million for the year ended December 31, 2015 and an accumulated deficit of \$119.7 million as of December 31, 2015, from expenses incurred in connection with our research programs and from general and administrative costs associated with our operations.

Other than royalties we are eligible to receive from sales of Glybera under our license to uniQure, which we do not expect to be significant in the near-term, we have not generated any royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales for the foreseeable future, if ever. We expect that our revenue in the near term will be substantially dependent on our collaboration agreements. Given the uncertain nature of clinical development of our current and future product candidates and the commercialization of current and future products, we cannot predict when or whether we will receive further milestone payments under our current or future collaboration agreements or whether we will be able to report either revenue or net income in future years.

We expect to continue to incur significant expenses and operating losses for at least the next 12 to 24 months. We anticipate that our expenses will increase substantially as we:

- continue our research and preclinical and clinical development of our product candidates;
- seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical trials;
- make milestone and other payments under our in-license agreements;
- maintain, protect and expand our intellectual property portfolio;
- attract, hire and retain skilled personnel; and
- create additional infrastructure to support our operations as a public company and otherwise.

#### Recent Developments

In February 2016, we announced that Dr. James R. Empfield joined Xenon as Senior Vice President, Drug Discovery. Dr. Empfield is responsible for leading drug discovery chemistry, manufacturing, and other preclinical activities that support the growth of our discovery and development pipeline.

We initiated a Phase 2 clinical trial of XEN801 in February 2016 in patients with moderate to severe acne. The Phase 2 clinical trial is a randomized, double-blind, multi-center, vehicle-controlled, parallel-group study to determine the safety, tolerability, efficacy and systemic exposure of XEN801 in approximately 150 patients with moderate to severe facial acne. Patients will apply XEN801 (or vehicle placebo) topically to their face for 12-weeks with a 4-week follow up. The primary efficacy endpoint is the percent change in total (inflammatory and non-inflammatory) lesion count from baseline to week 12. Secondary endpoints include the percent change in inflammatory and/or non-inflammatory lesions at different time points throughout the 12 week study as well as a number of Investigator's Global Assessment measures. We anticipate topline results in the fourth quarter of 2016.

#### Financial Operations Overview

##### Revenue

To date, our revenue has been primarily derived from collaboration and licensing agreements as well as, to a lesser extent, government funding. In addition, we have received nominal royalties from a diagnostic license. Other than royalties we are eligible to receive from sales of Glybera under our license to uniQure, which we do not expect to be significant in the near-term, we have not generated any royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales for the foreseeable future, if ever. We have entered into several collaboration agreements, the most significant of which, with respect to revenue, are described at “Business – Strategic Alliances” and “Note 9” of the financial statements included elsewhere in this Annual Report on Form 10-K.

The following table is a summary of revenue recognized from our current collaboration and licensing agreements for each of the years ended December 31, 2015, 2014 and 2013 (in thousands):

	Year Ended December 31,		
	2015	2014	2013
<b>uniQure:</b>			
Milestone payment	\$—	\$14	\$531
<b>Teva:</b>			
Recognition of upfront payment	10,897	12,255	13,143
Research funding	112	333	630
<b>Genentech:</b>			
Recognition of upfront payment	725	3,603	3,300
Research funding	3,589	4,248	4,514
Milestone payment	250	7,913	5,062
<b>Genome BC:</b>			
Research funding	—	—	172
Total collaboration revenue	\$15,573	\$28,366	\$27,352

Through December 31, 2015, we had recognized upfront fees and milestone payments totaling CAD\$1.1 million, pursuant to our sublicense and research agreement with uniQure. We are eligible to receive certain additional milestone payments of less than CAD\$1.0 million for Glybera and for each subsequent product, if any, developed pursuant to the agreement.

Pursuant to the terms of our collaborative development and license agreement with Teva, we received an upfront payment of \$41.0 million. We determined that the various deliverables under this agreement should be considered as a single unit of accounting. As such, the \$41.0 million upfront payment was recognized as revenue ratably over the expected period of research performance of pre-commercial activities, which was the three-year period from December 2012 through December 2015.

Pursuant to the terms of our December 2011 collaborative development and license agreement with Genentech, we received an upfront payment of \$10.0 million. We determined that the various deliverables under this agreement should be considered as a single unit of accounting. As such, the \$10.0 million upfront payment was recognized as revenue ratably over the expected period of research performance, which was the three-year period from December 2011 through December 2014. In September 2013, we recognized a \$5.1 million milestone payment for the selection of a compound for good laboratory practices, or GLP, toxicology studies. We recognized the milestone payment upon achievement in August 2013. In August 2014, we recognized a \$7.9 million milestone payment for the approval of the GDC-0276 Clinical Trial Application by Health Canada. We recognized the milestone payment upon achievement in August 2014.

Pursuant to the terms of our March 2014 agreement with Genentech, we received an upfront payment of \$1.5 million. We determined that the various deliverables under this agreement should be considered as a single unit of accounting. As such, the \$1.5 million upfront payment is being recognized as revenue ratably over the expected period of research performance, which is the two-year period from March 2014 to March 2016. In September 2015, we received a \$0.25 million milestone payment for the identification of a novel pain target under this agreement. We recognized the milestone payment upon achievement in September 2015.

As our other internal and partnered products are in various stages of clinical and preclinical development, we do not expect to generate any revenue from product sales other than from our share of revenue related to our agreement with uniQure, which we do not expect to be significant in the near-term, for at least the next several years. We expect that revenue for the next several years will be derived from our agreement with uniQure and our eligibility to receive a share of the compensation received by uniQure relating to the technology or products licensed by us, and full-time equivalents, or FTEs, and milestone payments under our current collaboration agreements and any additional collaboration agreements that we may enter into in the future. We cannot provide any assurance as to the extent or timing of future milestone payments or royalty payments or that we will receive any future payments at all.

We expect that any revenue we generate will fluctuate quarter to quarter as a function of the timing and amount of milestones and other payments from our existing collaborations and any future collaborations.

The following table is a summary of our deferred revenue for our collaboration and licensing agreements as of December 31, 2015, 2014 and 2013 (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Teva	\$—	\$10,897	\$24,691
Genentech	157	882	3,115
Total deferred revenue	\$157	\$11,779	\$27,806

We expect such deferred revenue remaining as of December 31, 2015 to be recognized as revenue in the fiscal year ending December 31, 2016 based on our accounting policy for revenue recognition for each collaboration agreement.

### Operating Expenses

The following table summarizes our operating expenses for the years ended December 31, 2015, 2014 and 2013 (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Research and development	\$15,152	\$11,768	\$12,303
General and administrative	9,786	5,496	5,341
Total operating expenses	\$24,938	\$17,264	\$17,644

### Research and Development Expenses

Research and development expenses represent costs incurred to conduct research on our product candidates in collaboration with Teva and Genentech, as well as further research and development of our other proprietary product candidates.

Research and development expenses consist of costs incurred in performing research and development activities, including salary, related benefits and stock-based compensation for employees engaged in scientific research and development, third-party contract costs relating to research, formulation, manufacturing, preclinical studies and clinical trial activities, third-party license and collaboration fees, laboratory consumables and allocated facility-related costs.

Project-specific expenses reflect costs directly attributable to our clinical development candidates and our preclinical candidates once nominated and selected for further development. All remaining research and development expenses are reflected in early-stage discovery programs. At any given time, we have several active early-stage research and drug discovery programs. Our personnel and infrastructure are typically deployed over multiple projects and are not directly linked to any individual internal early-stage research or drug discovery program. Therefore, we do not maintain financial information for our internal early-stage research and internal drug discovery programs on a project-specific basis.

We expense all research and development costs as incurred. We expect that our research and development expenses will increase in the future as we advance our proprietary product candidates through clinical development, advance our internal drug discovery programs into preclinical development and continue our early-stage research. The increase in expense will likely include added personnel and third-party contracts related to research, formulation, manufacturing, preclinical studies and clinical trial activities as well as third-party license and collaboration fees and laboratory consumables.

Clinical development timelines, likelihood of regulatory approval and commercialization and associated costs are uncertain and difficult to estimate and can vary significantly. We anticipate determining which research and development projects to pursue as well as the level of funding available for each project based on the scientific research and preclinical and clinical results of each product candidate and related regulatory action. We expect our research and development expenses to continue to represent our largest category of operating expense for at least the next 12 to 24 months.

## General and Administrative Expenses

General and administrative expenses consist primarily of salary, related benefits and stock-based compensation of our executive, finance, business development and administrative functions, travel expenses, allocated facility-related costs not otherwise included in research and development expenses, director compensation and professional fees for auditing, tax and legal services, including legal expenses for intellectual property protection. Following our initial public offering in November 2014, or IPO, we have been incurring additional general and administrative expenses as a public company, including costs of additional personnel, additional professional fees for audit, accounting and legal services, director compensation, enhanced business and accounting systems, costs related to investor relations and increased premiums for directors' and officers' liability insurance.

General and administrative expenses for the year ended December 31, 2015 also include fair value adjustments upon the reclassification of stock option awards granted to directors and certain consultants to liability classification in the first quarter of 2015 and a subsequent reclassification of those stock options back to equity in September 2015, due to a change in the denomination of pay of directors and certain consultants in the third quarter. We do not expect that general and administrative expenses will be impacted by similar adjustments in future periods.

We expect that general and administrative expenses will increase in the future as we expand our operating activities to support increased research and development activities, and the potential build of commercial infrastructure for our option for co-promotion of TV-45070 in the U.S., if and when regulatory approval is received.

## Other Income (Expense)

**Interest Income.** Interest income consists of income earned on our cash and investment balances. Our interest income has not been significant due to the levels of cash and investment balances and low interest earned on such balances. We anticipate that our interest income will continue to fluctuate depending on timing of payments from collaborative partners, our cash and investment balances, and interest rates.

**Foreign Exchange Gain (Loss).** On January 1, 2015, our functional currency changed from the Canadian dollar to the U.S. dollar based on our analysis of the changes in the primary economic environment in which we operate. For the year ended December 31, 2015, net foreign exchange gains and losses consisted of gains and losses from the impact of foreign exchange fluctuations on our monetary assets and liabilities that were denominated in currencies other than the U.S. dollar (principally the Canadian dollar) whereas for the year ended December 31, 2014, net foreign exchange gains and losses consisted of gains and losses from the impact of foreign exchange fluctuations on our monetary assets and liabilities that were denominated in currencies other than the Canadian dollar (principally the U.S. dollar). We will continue to incur substantial expenses in Canadian dollars and will remain subject to risks associated with foreign currency fluctuations. See "Quantitative and Qualitative Disclosures About Market Risk – Foreign Currency Exchange Risk" below for additional information.

## Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in conformity with generally accepted accounting principles in the U.S., or U.S. GAAP. The preparation of our financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the revenue and expenses incurred during the reported periods. We base estimates on our historical experience, known trends and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

The significant accounting policies that we believe to be most critical in fully understanding and evaluating our financial results are revenue recognition, research and development costs and stock-based compensation. See “Note 3” of the financial statements for additional information.

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Revenue recognition:

Revenue recognition is a critical accounting estimate due to the magnitude and nature of the revenues we receive.

We are eligible to receive non-refundable upfront payments, funding for research and development services, milestone payments, other contingent payments and royalties under our various collaboration agreements. In assessing the appropriate revenue recognition related to a collaboration agreement, we first determine whether an arrangement includes multiple elements, such as the delivery of intellectual property rights and research and development services. Revenues associated with multiple element arrangements are attributed to the various elements based on their relative fair values or are recognized as a single unit of accounting when relative fair values are not determinable.

Non-refundable upfront payments are recorded as deferred revenue on the balance sheet and are recognized as collaboration revenue over the estimated period of research performance that is consistent with the terms of the research and development obligations contained in the collaboration agreement. We need to make estimates as to what period the services will be delivered as these payments are deferred and amortized into collaboration revenue over the estimated period of our ongoing involvement. The actual period of our ongoing involvement may differ from the estimated period determined at the time the payment is initially received and recorded as deferred revenue. This may result in a different amount of revenue that should have been recorded in the period and a longer or shorter period of revenue amortization. When an estimated period changes, we amortize the remaining deferred revenue over the estimated remaining time to completion.

We recognize funding related to full-time equivalent staffing funded through collaboration agreements as revenue on a gross basis as we perform or deliver such related services in accordance with the agreement terms, provided that we will receive payment for such services upon standard payment terms.

We recognize revenue contingent upon our achievement of a milestone in its entirety, in the period the milestone is achieved, only if the milestone meets certain criteria and is considered to be substantive. Payments received upon the occurrence of milestones that are non-substantive are deferred and recognized as revenue over the estimated period of performance applicable to the associated collaborative agreement.

Research and development costs:

Research and development costs is a critical accounting estimate due to the magnitude of and the many assumptions that are required to calculate third-party accrued and prepaid research and development expenses.

We incur development activity costs, such as preclinical costs, manufacturing costs and clinical trial costs paid to contract research organizations, investigators and other vendors who conduct certain product development activities on our behalf. The amount of expenses recognized in a period related to service agreements is based on estimates of the work performed using an accrual basis of accounting. These estimates are based on patient enrollment, services provided and goods delivered, contractual terms and experience with similar contracts. We monitor these factors and adjust our estimates accordingly.

Stock-based compensation:

Stock-based compensation is a critical accounting estimate due to the magnitude of and the many assumptions that are required to calculate stock-based compensation expense.

We grant stock options to employees, directors and consultants pursuant to our stock option plan. Compensation expense is recorded for stock options issued to employees and non-employees using the fair value method. We

calculate the fair value of stock options using the Black-Scholes option-pricing model which requires that certain assumptions, including the expected life of the option, expected volatility of the stock and expected forfeitures, be estimated at the time that the options are granted.

Prior to our IPO, our shares did not have a readily available market; therefore, we lack company-specific historical and implied volatility information. Consequently, we estimated the expected volatility of our stock options based on a historical volatility analysis of peers that are similar with respect to industry, stage of life cycle, size, and financial leverage. The expected term of our stock options has been determined utilizing the “simplified” method. Under this method, the expected term represents the average of the vesting period and the contractual term. We also make an estimate for stock option forfeitures at the time of grant and revise this estimate in subsequent periods if actual forfeitures differ. We amortize the fair value of stock options using the straight-line method over the vesting period of the options.

## Results of Operations

## Comparison of Years Ended December 31, 2015 and 2014

The following table summarizes the results of our operations for the years ended December 31, 2015 and 2014 together with changes in those items (in thousands):

	Year Ended December 31,		Change
	2015	2014	2015 vs. 2014 Increase/(Decrease)
Collaboration revenue	\$ 15,573	\$ 28,366	\$ (12,793 )
Royalties	4	4	—
Research and development expenses	15,152	11,768	3,384
General and administrative expenses	9,786	5,496	4,290
Other:			
Interest income	542	568	(26 )
Foreign exchange gain (loss)	(6,933 )	1,344	(8,277 )
Net income (loss)	\$ (15,752 )	\$ 13,018	\$ (28,770 )

## Revenue

We recognized revenue of \$15.6 million for the year ended December 31, 2015 compared to \$28.4 million for the year ended December 31, 2014, a decrease of \$12.8 million. In 2014, we recognized a \$7.9 million milestone payment from Genentech for the approval of the GDC-0276 Clinical Trial Application by Health Canada as well as revenue related to the upfront payment from the December 2011 collaborative development and license agreement with Genentech which was fully recognized by December 2014. The remaining decrease was due to less FTE funding from Genentech and Teva and the change in the foreign exchange rate between the U.S. and Canadian dollar.

## Research and Development Expenses

The following table summarizes research and development expenses for the years ended December 31, 2015 and 2014 together with changes in those items (in thousands):

	Year Ended December 31,		Change
	2015	2014	2015 vs. 2014 Increase/(Decrease)
Teva collaboration (TV-45070) expenses	\$ 136	\$ 1,115	\$ (979 )
Genentech collaboration (GDC-0276 and GDC-0310)			
expenses	2,626	4,788	(2,162 )
XEN801 expenses	4,446	1,742	2,704
Preclinical and discovery program expenses	7,944	4,123	3,821

Total research and development expenses	\$ 15,152	\$ 11,768	\$ 3,384
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Research and development expenses were \$15.2 million for the year ended December 31, 2015 as compared to \$11.8 million for the year ended December 31, 2014. The increase of \$3.4 million was primarily attributable to increased spending on our preclinical and discovery programs, mostly related to our Nav1.6 sodium channel inhibitor program, as well as additional expenses for our XEN801 program in preparation for clinical development which began in September 2015. These increases were partially offset by decreases in Teva and Genentech collaboration expenses and the change in the foreign exchange rate between the U.S. and Canadian dollar.

#### General and Administrative Expenses

The following table summarizes general and administrative expenses for the years ended December 31, 2015 and 2014 together with changes in those items (in thousands):

	Change		
	Year Ended December 31, 2015	2014	2015 vs. 2014 Increase/(Decrease)
General and administrative expenses	\$ 9,786	\$ 5,496	\$ 4,290

General and administrative expenses were \$9.8 million for the year ended December 31, 2015 compared to \$5.5 million for the year ended December 31, 2014, an increase of \$4.3 million. During 2015, we recognized a \$1.7 million expense due to a fair value adjustment upon the reclassification of stock option awards granted to directors and certain consultants to liability classification in the first quarter of 2015 and the subsequent change in fair value until the options were reclassified back to equity in the third quarter of 2015. The remaining change is due to additional expenses incurred as a public company, including costs of additional personnel, additional professional fees for audit, accounting and legal services, director fees, enhanced business and accounting systems, costs related to investor relations and increased premiums for directors' and officers' liability insurance as well as one-time severance costs resulting from an internal reorganization that occurred in the second quarter of 2015 and acceleration of stock based compensation expense for certain consultants, partially offset by the change in the foreign exchange rate between the U.S. and Canadian dollar.

#### Other Income (Expense)

The following table summarizes our other income (expense) for the years ended December 31, 2015 and 2014 together with changes in those items (in thousands):

	Change		
	Year Ended December 31,		2015 vs. 2014
	2015	2014	Increase/(Decrease)
Other income (expense):	\$ (6,391 )	\$ 1,912	\$ (8,303 )

Other expense was \$6.4 million for the year ended December 31, 2015 as compared to other income of \$1.9 million for the year ended December 31, 2014. The change of \$8.3 million was primarily driven by unrealized foreign exchange losses arising largely from the translation of cash and cash equivalents denominated in Canadian dollars to U.S. dollars and a 16% decrease in the value of the Canadian dollar during the year.

#### Comparison of Years Ended December 31, 2014 and 2013

The following table summarizes the results of our operations for the years ended December 31, 2014 and 2013 together with changes in those items (in thousands):

	Change		
	Year Ended December 31,		2014 vs. 2013
	2014	2013	Increase/(Decrease)
Collaboration revenue	\$ 28,366	\$ 27,352	\$ 1,014
Royalties	4	4	—
Research and development expenses	11,768	12,303	(535 )
General and administrative expenses	5,496	5,341	155
Other:			
Interest income	568	338	230
Interest expense	—	(64 )	64

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Foreign exchange gain	1,344	2,035	(691	)
Gain on write-off and disposal of assets	—	11	(11	)
Net income	\$ 13,018	\$ 12,032	\$ 986	

Revenue

We recognized revenue of \$28.4 million for the year ended December 31, 2014 compared to \$27.4 million for the year ended December 31, 2013, an increase of \$1.0 million. The increase was primarily attributable to a \$7.9 million milestone payment from Genentech recognized in August 2014 for the approval of the GDC-0276 Clinical Trial Application by Health Canada and recognition of revenues related to the upfront payment from the March 2014 pain genetics collaboration with Genentech. These increases were partially offset by a \$5.1 million milestone payment recognized in August 2013 from Genentech and the change in the foreign exchange rate between the U.S. and Canadian dollar.

## Research and Development Expenses

The following table summarizes research and development expenses for the years ended December 31, 2014 and 2013 together with changes in those items (in thousands):

	Year Ended December 31,		Change
	2014	2013	2014 vs. 2013 Increase/(Decrease)
Teva collaboration (TV-45070) expenses	\$ 1,115	\$ 1,005	\$ 110
Genentech collaboration (GDC-0276) expenses	4,788	5,072	(284 )
Other collaboration expenses	—	133	(133 )
Preclinical and discovery program expenses	5,865	6,093	(228 )
Total research and development expenses	\$ 11,768	\$ 12,303	\$ (535 )

Research and development expenses were \$11.8 million for the year ended December 31, 2014 as compared to \$12.3 million for the year ended December 31, 2013. The decrease of \$0.5 million was primarily attributable to the change in the foreign exchange rate between the U.S. and Canadian dollar as the majority of our research and development expenses are incurred in Canadian dollars. Additionally, there was a decrease in preclinical and discovery program expenses as XEN701 was discontinued in late 2013, partially offset by an increase in spending for our other early stage research programs.

## General and Administrative Expenses

The following table summarizes general and administrative expenses for the years ended December 31, 2014 and 2013 together with changes in those items (in thousands):

	Year Ended December 31,		Change
	2014	2013	2014 vs. 2013 Increase/(Decrease)
General and administrative expenses	\$ 5,496	\$ 5,341	\$ 155

General and administrative expenses were \$5.5 million for the year ended December 31, 2014 compared to \$5.3 million for the year ended December 31, 2013. This increase was primarily due to an increase in finance-related salaries and benefits and in overhead expenses. The increase was partially offset by the change in the foreign exchange rate between the U.S. and Canadian dollar as the majority of our general and administrative expenses are incurred in Canadian dollars.

## Other Income

The following table summarizes our other income for the years ended December 31, 2014 and 2013 together with changes in those items (in thousands):

	Year Ended December 31,		Change
	2014	2013	2014 vs. 2013 Increase/(Decrease)
Other income:	\$ 1,912	\$ 2,320	\$ (408 )

Other income was \$1.9 million for the year ended December 31, 2014 as compared to \$2.3 million for the year ended December 31, 2013, a decrease of \$0.4 million. The decrease was primarily attributable to the change in the foreign exchange rate between the U.S. and Canadian dollar, partially offset by an increase in interest income attributable to an increase in interest rates and balances of savings accounts.

#### Liquidity and Capital Resources

To date, we have financed our operations primarily through funding received from collaboration and license agreements, private placements of our common and preferred shares and our IPO, as well as through the receipt of government funding. As of December 31, 2015, we had cash and cash equivalents and marketable securities of \$58.7 million. We received \$38.5 million of proceeds, net of underwriting discounts and commissions but before offering expenses, from our IPO and \$4.1 million of proceeds, net of underwriters' fees but before offering expenses, from the concurrent private placement to an affiliate of Genentech. Our IPO and concurrent private placement each closed in November 2014.



We have incurred significant operating losses since inception. We had a \$15.8 million net loss for the year ended December 31, 2015 and an accumulated deficit of \$119.7 million from inception through December 31, 2015. We expect to continue to incur significant expenses in excess of our revenue and expect to incur operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We expect to continue to incur significant expenses and operating losses for the foreseeable future as we continue our research and preclinical and clinical development of our product candidates; expand the scope of our current studies for our product candidates; initiate additional preclinical, clinical or other studies for our product candidates, including under our collaboration agreements; change or add additional manufacturers or suppliers; seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical studies; seek to identify and validate additional product candidates; acquire or in-license other product candidates and technologies; make milestone or other payments under our in-license agreements including, without limitation, our agreements with the University of British Columbia, or UBC, and the Memorial University of Newfoundland, or MUN; maintain, protect and expand our intellectual property portfolio; attract and retain skilled personnel; establish a sales, marketing and distribution infrastructure to commercialize any products for which we or one of our collaborators may obtain marketing approval, and maintain commercial rights; create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and experience any delays or encounter issues with any of the above.

Until such time as we can generate substantial product revenue, if ever, we expect to finance our cash needs through a combination of collaboration agreements and equity or debt financings. Except for any obligations of our collaborators to reimburse us for research and development expenses or to make milestone payments under our agreements with them, we do not have any committed external sources of capital. To the extent that we raise additional capital through the future sale of equity or debt, the ownership interest of our shareholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common shareholders. If we raise additional funds through collaboration agreements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our future capital requirements are difficult to forecast and will depend on many factors, including:

- the number and characteristics of the future product candidates we pursue;
  - the scope, progress, results and costs of independently researching and developing any of our future product candidates, including conducting preclinical research and clinical trials;
- whether our existing collaborations continue to generate substantial milestone payments and, ultimately, royalties on future approved products for us;
- the timing of, and the costs involved in, obtaining regulatory approvals for any future product candidates we develop independently;
- the cost of future commercialization activities, if any, including activities required pursuant to our option to co-promote TV-45070, if exercised by us, and the cost of commercializing any future products we develop independently that are approved for sale;
- the cost of manufacturing our future product candidates and products, if any;
- our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the costs of preparing, filing, prosecuting, maintaining, defending and enforcing patents, including litigation costs and the outcome of such litigation; and
-

the timing, receipt and amount of sales of, or royalties on, Glybera or our collaborators' product candidates, and our future products, if any.

Based on our research and development plans and our timing expectations related to the progress of our programs, we expect that our existing cash and cash equivalents and marketable securities as of the date of this report, and research funding that we expect to receive under our existing collaborations, will enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 to 24 months. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect. Additionally, the process of testing drug candidates in clinical trials is costly, and the timing of progress in these trials remains uncertain.

## Cash Flows

The following table shows a summary of our cash flows for the years ended December 31, 2015, 2014 and 2013 (in thousands):

	Year Ended December 31,		
	2015	2014	2013
Net cash provided by (used in) operating activities	\$(18,103)	\$266	\$(3,322 )
Net cash provided by (used in) investing activities	10,194	(3,244 )	(11,472)
Net cash provided by (used in) financing activities	278	41,124	(4,391 )

## Operating Activities

Net cash used by operating activities totaled \$18.1 million in 2015, compared to \$0.3 million of cash provided by operating activities for 2014. The change was primarily related to the increase in operating expenses in 2015, \$3.2 million in payments to Medpace, Inc., or Medpace, mostly for future clinical development services, a \$7.9 million milestone payment recognized from Genentech in August 2014, a \$1.5 million upfront payment received from Genentech for the pain genetics collaboration entered into in March 2014 and \$0.9 million less FTE funding from Genentech and Teva as compared to the same period in 2014.

Net cash provided by operating activities totaled \$0.3 million in 2014, compared to \$3.3 million of cash used by operating activities for 2013. The change was primarily related to an increase in milestone revenue from Genentech in 2014 as compared to the prior year and the timing of cash payments on trade payables.

Net cash used by operating activities totaled \$3.3 million in 2013. Our net income of \$12.0 million was offset by a significant decrease in deferred revenue and other changes in working capital.

## Investing Activities

Net cash provided by investing activities totaled \$10.2 million in 2015, compared to \$3.2 million of cash used in investing activities for 2014. The change was driven primarily by the redemption of marketable securities in 2015 and a decrease in the purchase of property, plant and equipment.

Net cash used in investing activities totaled \$3.2 million in 2014, compared to \$11.5 million of cash used in investing activities for 2013. The change was driven primarily by a decrease in net investment of marketable securities, partially offset by an increase in the purchase of property, plant and equipment.

Net cash used in investing activities totaled \$11.5 million and consisted primarily of purchases of marketable securities, partially offset by proceeds from marketable securities.

## Financing Activities

Net cash provided by financing activities totaled \$0.3 million in 2015, compared to \$41.1 million for 2014. Net cash provided by financing activities in 2015 consisted exclusively of proceeds from the issuance of common shares from the exercise of stock options whereas net cash provided by financing activities in 2014 was driven primarily by proceeds from the issuance of common shares related to our IPO and concurrent private placement in November 2014.

Net cash provided by financing activities totaled \$41.1 million in 2014, compared to \$4.4 million of cash used in financing activities for 2013. Net cash provided by financing activities in 2014 was driven primarily by proceeds from the issuance of common shares related to our IPO and concurrent private placement in November 2014 whereas the net cash used in financing activities in 2013 was driven primarily by deferred financing costs related to the IPO and repayment of a note we issued to a former collaborator.

#### Contractual Obligations and Commitments

The following summarizes our significant contractual obligations as of December 31, 2015 (in thousands):

		Less Than	More Than		
		1 Year	1 To 3 Years	3 To 5 Years	5 Years
Contractual Obligations	Total				
Operating leases (1)	\$6,594	\$972	\$2,162	\$2,187	\$1,273

(1) Represents future minimum lease payments under an operating lease in effect as of December 31, 2015 for our current facility in Burnaby, British Columbia, Canada.

The contractual obligations table above excludes a priority access agreement entered into in August 2015 with Medpace for the provision of certain clinical development services. Under the terms of the agreement, we committed to using Medpace non-exclusively for clinical development services over the five year term of the agreement. In consideration for priority access to Medpace resources and preferred service rates, we committed to \$7.0 million of services over the term of the agreement, \$1.7 million of which was prepaid upon signing of the agreement and an additional \$1.3 million was paid in December 2015. Any portion of the \$3.0 million payment made during 2015 that is not used within the first three years of the agreement term will be forfeited to Medpace. If we do not meet the commitment to retain Medpace for \$7.0 million of services during the term of the agreement, we agreed to give Medpace the exclusive right to perform all of our subsequent outsourced clinical development work until such \$7.0 million commitment has been satisfied, subject to the availability of appropriate Medpace resources and reasonable service rates. If we decide not to retain Medpace for the provision of clinical development services, we may satisfy our obligations under the priority access agreement by paying Medpace an amount equal to half of the unsatisfied portion of the \$7.0 million minimum commitment. See “Note 10(b)” and “Note 12” of the financial statements for additional information.

Also excluded from the table above are potential future payments we may be required to make if we elect to opt into the co-development arrangement under our collaboration with Merck or the co-promotion for TV-45070 under our collaboration with Teva. Our potential payment obligations in the single-digit percentage range to UBC related to amounts we receive from sales of Glybera are also excluded from the table. Additionally, the table does not include our potential royalty and milestone payment obligations to MUN pursuant to the Restated Collaborative Research & License Agreement by and between us and MUN dated December 2006. Pursuant to this agreement, we are obligated to pay MUN certain milestone payments and a single-digit percentage royalty of net sales for products that we sell directly and a single-digit percentage of royalties we receive from sales on products under our pain program.

#### Inflation

We do not believe that inflation has had a material effect on our business, financial condition or results of operations in the last three fiscal years.

#### Off-Balance Sheet Arrangements

We do not engage in any off-balance sheet financing activities. We do not have any interest in entities referred to as variable interest entities, which include special purposes entities and other structured finance entities.

#### Related Party Transactions

For a description of our related party transactions, see “Certain Relationships and Related Transactions, and Director Independence.”

#### Outstanding Share Data

As of March 4, 2016, we had 14,401,582 common shares issued and outstanding and outstanding stock options to purchase an additional 1,753,022 common shares.

#### Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued amendments to clarify the principles of recognizing revenue and to develop a common revenue standard that would remove inconsistencies in revenue requirements, leading to improved comparability of revenue recognition practices across entities and industries. The

amendments stipulate that an entity should recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. Additional disclosure will also be required about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments, and assets recognized from costs incurred to obtain or fulfill a contract. In August 2015, the FASB issued an update deferring the effective date of the new revenue standard by one year. The new guidance will be effective for public entities for fiscal years beginning after December 15, 2017 instead of the originally contemplated effective date of December 15, 2016. We are currently evaluating the new guidance to determine the impact it will have on our financial position, results of operations and cash flows.

In August 2014, the FASB issued amendments requiring management to assess an entity's ability to continue as a going concern. For each reporting period, management will be required to evaluate whether there are conditions or events that raise substantial doubt about a company's ability to continue as a going concern within one year from the date the financial statements are issued. These amendments will be effective for public entities for the annual period ending after December 15, 2016, and for annual periods and interim periods thereafter. The adoption of these amendments in fiscal 2017 is not expected to have a material impact on our financial statements.

The Jumpstart Our Business Startups Act of 2012, or JOBS Act, provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. However, we previously chose to "opt out" of such extended transition period, and as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of the JOBS Act provides that our decision to opt out of the extended transition period for complying with new or revised accounting standards is irrevocable.

#### Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to various market risks in the ordinary course of our business, including changes in interest rates and currency exchange rates. Market risk is the potential loss arising from adverse changes in interest rates and exchange rates.

##### Foreign Currency Exchange Risk

On January 1, 2015, our functional currency changed from the Canadian dollar to the U.S. dollar based on our analysis of the changes in the primary economic environment in which we operate.

The principal market risk we face is foreign currency exchange rate risk. We face this risk, in part, as a result of entering into transactions denominated in currencies other than U.S. dollars, particularly those denominated in Canadian dollars. We also hold non-U.S. dollar denominated cash and cash equivalents, marketable securities, accounts receivable and accounts payable, which are denominated in Canadian dollars.

Changes in foreign currency exchange rates can create significant foreign exchange gains or losses to us. Our current foreign currency risk is with the Canadian dollar, as a majority of our non-U.S. dollar denominated expenses are denominated in Canadian dollars and the majority of our cash and cash equivalents and marketable securities are held in Canadian dollars. To limit our exposure to volatility in currency markets, we estimate our anticipated expenses that will be denominated in Canadian and U.S. dollars and then purchase a corresponding amount of Canadian or U.S. dollars at the current spot rate. Once these estimated expense amounts are acquired, we do not hedge our exposure and thus assume the risk of future gains or losses on the amounts of Canadian dollars held. At December 31, 2015, we held cash and cash equivalents and marketable securities of \$40.8 million denominated in Canadian dollars. A hypothetical 10% increase (decrease) in the value of the Canadian dollar would result in a foreign exchange gain (loss) of \$4.1 million being recorded in the Statement of Operations and Comprehensive Income (Loss) on the translation of these Canadian dollar cash and cash equivalent and marketable securities balances into the U.S. dollar functional currency.

##### Interest Rate Risk

An additional market risk we face is interest rate risk. We had cash and cash equivalents and marketable securities of \$58.7 million as of December 31, 2015. The goals of our investment policy are liquidity and capital preservation; we do not enter into investments for trading or speculative purposes and have not used any derivative financial instruments to manage our interest rate exposure. We believe that we do not have any material exposure to changes in the fair value of these assets as a result of changes in interest rates due to the short term nature of our cash and cash equivalents and marketable securities. Declines in interest rates, however, would reduce future investment income. A 10% change in interest rates during any of the periods presented would not have had a material impact on our financial statements. Such interest-earning instruments carry a degree of interest rate risk. We had no outstanding debt as of December 31, 2015.



Item 8. Financial Statements and Supplementary Data  
XENON PHARMACEUTICALS INC.

Index to Financial Statements

Year ended December 31, 2015

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Report of INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Shareholders and Directors of Xenon Pharmaceuticals Inc.

We have audited the accompanying balance sheets of Xenon Pharmaceuticals Inc. as of December 31, 2015 and December 31, 2014 and the related statement of operations and comprehensive income (loss), shareholders' equity (deficit) and cash flows for each of the years in the three-year period ended December 31, 2015. These financial statements are the responsibility of Xenon Pharmaceuticals Inc.'s management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Xenon Pharmaceuticals Inc. as of December 31, 2015 and December 31, 2014, and its results of operations and its cash flows for each of the years in the three-year period ended December 31, 2015 in conformity with US generally accepted accounting principles.

/s/ KPMG LLP

Chartered Professional Accountants

March 8, 2016

Vancouver, Canada

## XENON PHARMACEUTICALS INC.

## Balance Sheets

(Expressed in thousands of U.S. dollars except share amounts)

	December 31, 2015	December 31, 2014
<b>Assets</b>		
<b>Current assets:</b>		
Cash and cash equivalents	\$58,651	\$72,026
Marketable securities	—	12,015
Accounts receivable	315	215
Prepaid expenses and other current assets	1,900	686
	60,866	84,942
Prepaid expenses, long term	1,094	—
Property, plant and equipment, net (note 5)	1,989	2,476
<b>Total assets</b>	<b>\$63,949</b>	<b>\$87,418</b>
<b>Liabilities and shareholders' equity</b>		
<b>Current liabilities:</b>		
Accounts payable and accrued expenses (note 6)	2,625	2,664
Deferred revenue	157	11,622
	2,782	14,286
Deferred revenue, less current portion	—	157
Deferred tenant inducements	133	196
	\$2,915	\$14,639
<b>Shareholders' equity:</b>		
Common shares, without par value; unlimited shares authorized; issued and		
outstanding: 14,385,336 (December 31, 2014 - 14,181,333) (note 7b)	148,634	147,157
Additional paid-in capital	33,083	30,346
Accumulated deficit	(119,693)	(103,734)
Accumulated other comprehensive loss	(990)	(990)
	\$61,034	\$72,779
<b>Total liabilities and shareholders' equity</b>	<b>\$63,949</b>	<b>\$87,418</b>
Collaboration agreements (note 9)		
Commitments and contingencies (note 10)		

The accompanying notes are an integral part of these financial statements.



## XENON PHARMACEUTICALS INC.

## Statements of Operations and Comprehensive Income (Loss)

(Expressed in thousands of U.S. dollars except share and per share amounts)

	Year Ended December 31,		
	2015	2014	2013
<b>Revenue:</b>			
Collaboration revenue (note 9)	\$15,573	\$28,366	\$27,352
Royalties	4	4	4
	15,577	28,370	27,356
<b>Operating expenses:</b>			
Research and development	15,152	11,768	12,303
General and administrative	9,786	5,496	5,341
	24,938	17,264	17,644
Income (loss) from operations	(9,361 )	11,106	9,712
<b>Other income (expense):</b>			
Interest income	542	568	338
Interest expense	—	—	(64 )
Foreign exchange gain (loss)	(6,933 )	1,344	2,035
Gain on write-off and disposal of assets	—	—	11
Net income (loss)	(15,752 )	13,018	12,032
Net income attributable to participating securities	—	—	8,199
Net income (loss) attributable to common shareholders	\$(15,752 )	\$13,018	\$3,833
<b>Net income (loss) per common share (note 3m):</b>			
Basic	\$(1.10 )	\$4.11	\$2.87
Diluted	\$(1.10 )	\$3.28	\$1.91
<b>Weighted-average shares outstanding (note 3m):</b>			
Basic	14,281,837	3,165,572	1,337,662
<b>Effects of dilutive securities</b>			
Stock options	—	798,225	659,167
Subscription rights	—	—	12,277
Diluted	14,281,837	3,963,797	2,009,106
<b>Other comprehensive income (loss):</b>			
Foreign currency translation adjustment	—	(3,501 )	(1,236 )
Comprehensive income (loss)	(15,752 )	9,517	10,796

The accompanying notes are an integral part of these financial statements.



XENON pharmaceuticals INC.

Statement of Shareholders' Equity (Deficit)

(Expressed in thousands of U.S. dollars except share amounts)

	Series A convertible preferred shares		Series B convertible preferred shares		Series E convertible preferred shares		Common shares		Additional paid-in capital	Accumulated deficit	Accumulated income (loss) other comprehensive
	Shares	Amount	Shares	Amount	Shares	Amount	Shares	Amount			
of											
1,	1,151,468	\$2,939	994,885	\$8,683	4,322,126	\$90,866	1,330,696	\$6,008	29,164	\$(128,784)	\$3,747
for										12,032	
											(1,236)
n									575		
on											
									73		
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(1) At December 31, 2015, our accumulated other comprehensive loss is entirely related to historical cumulative translation adjustments from the application of U.S. dollar reporting when the functional currency of the Company was the Canadian dollar as described in note 3n.

The accompanying notes are an integral part of these financial statements.

## XENON PHARMACEUTICALS INC.

## Statements of Cash Flows

(Expressed in thousands of U.S. dollars)

	Year Ended December 31,		
	2015	2014	2013
<b>Operating activities:</b>			
Net income (loss)	\$(15,752)	\$13,018	\$12,032
<b>Items not involving cash:</b>			
Depreciation and amortization	1,038	738	705
Gain on write-off of assets	—	—	(11 )
Stock-based compensation	3,729	760	575
Non-cash compensation on issuance of subscription rights	—	—	73
Deferred tenant inducements	(63 )	(66 )	(115 )
Unrealized foreign exchange loss	6,902	72	94
<b>Changes in operating assets and liabilities:</b>			
Accounts receivable	(107 )	209	(76 )
Prepaid expenses, and other current assets	(1,214 )	(573 )	(14 )
Prepaid expenses, long term	(1,094 )	—	—
Accounts payable and accrued expenses	80	518	(228 )
Deferred revenue	(11,622)	(14,410 )	(16,357)
Net cash provided by (used in) operating activities	(18,103)	266	(3,322 )
<b>Investing activities:</b>			
Purchases of property, plant and equipment	(551 )	(1,529 )	(156 )
Sale of property, plant and equipment	—	—	10
Purchase of marketable securities	—	(15,254 )	(17,876)
Proceeds from marketable securities	10,745	13,539	6,550
Net cash provided by (used in) investing activities	10,194	(3,244 )	(11,472)
<b>Financing activities:</b>			
Note payable	—	—	(1,701 )
Deferred financing fees	—	(1,533 )	(2,739 )
Proceeds from issuance of common shares	278	42,657	49
Net cash provided by (used in) financing activities	278	41,124	(4,391 )
Effect of exchange rate changes on cash and cash equivalents	(5,744 )	(4,070 )	(3,027 )
Increase (decrease) in cash and cash equivalents	(13,375)	34,076	(22,212)
Cash and cash equivalents, beginning of year	72,026	37,950	60,162
Cash and cash equivalents, end of year	\$58,651	\$72,026	\$37,950
<b>Supplemental disclosures:</b>			
Interest paid	\$—	\$—	\$201
Interest received	659	574	279

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Supplemental disclosures of non-cash transactions:

Issuance of common shares on conversion of subscription rights	—	124	45
Financing fees included in accounts payable and accrued liabilities	—	39	—
Fair value of options exercised on a cashless basis	744	—	—
Conversion of convertible preferred shares into common shares	—	102,488	—

The accompanying notes are an integral part of these financial statements.

XENON PHARMACEUTICALS INC.

Notes to Financial Statements

(Expressed in thousands of U.S. dollars except share and per share amounts)

1. Nature of the business:

Xenon Pharmaceuticals Inc. (the “Company”), incorporated in 1996 under the British Columbia Business Corporations Act and continued federally in 2000 under the Canada Business Corporation Act, is a clinical-stage biopharmaceutical company discovering and developing a pipeline of differentiated therapeutics for orphan indications that it intends to commercialize on its own, and for larger market indications that it intends to partner with global pharmaceutical companies.

On October 1, 2014, the Company effected a 1 for 4.86 reverse share split of its common shares and Series A, B and E redeemable convertible preferred shares. At the time of the consolidation, there were no outstanding Series C and D preferred shares and therefore such series were not included in the consolidation. Accordingly, (i) every 4.86 common shares were combined into one common share, (ii) every 4.86 redeemable Series A, B and E convertible preferred shares were combined into one redeemable convertible preferred share, (iii) the number of common shares into which each outstanding subscription right was exchangeable into common shares were proportionately decreased on a 1 for 4.86 basis, (iv) the number of common shares into which each outstanding option to purchase common shares was exercisable were proportionately decreased on a 1 for 4.86 basis, and (v) the exercise price for each such outstanding option to purchase common shares was proportionately increased on a 1 for 4.86 basis. All of the share numbers, share prices, and exercise prices prior to October 1, 2014 have been adjusted, on a retroactive basis, to reflect this 1 for 4.86 reverse share split.

On November 10, 2014, the Company completed an initial public offering (“IPO”) of 4,600,000 of its common shares at a price to the public of \$9.00 per share. On November 10, 2014, the Company also completed a private placement, in which the Company issued 495,000 of its common shares to an affiliate of Genentech, Inc. (“Genentech”) at a price of \$9.00 per share. Immediately prior to the closing of the IPO, all outstanding convertible preferred shares were converted into 7,725,924 common shares and 10,201 outstanding subscription rights were converted into 10,201 common shares (note 7a). Following the IPO, there were no preferred shares or subscription rights outstanding.

2. Basis of presentation:

These financial statements are presented in U.S. dollars.

The accompanying audited financial statements of the Company have been prepared in accordance with United States generally accepted accounting principles (“U.S. GAAP”).

These audited financial statements reflect all adjustments, consisting of normal recurring adjustments, which, in the opinion of management, are necessary for a fair presentation of the financial position of the Company as at December 31, 2015 and the result of operations and cash flows for all periods presented.

3. Significant accounting policies:

(a) Use of estimates:

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. Significant areas of estimates include, but are not limited to, the timing of revenue recognition, the determination of stock-based compensation and the amounts recorded as accrued liabilities. Actual results could differ materially from those estimates. Estimates and assumptions are reviewed quarterly. All revisions to accounting estimates are recognized in the period in which the estimates are revised and in any future periods affected.

(b) Cash and cash equivalents:

Cash equivalents are highly liquid investments that are readily convertible into cash with terms to maturity of three months or less when acquired. Cash equivalents are recorded at cost plus accrued interest. The carrying value of these cash equivalents approximates their fair value.

(c) Marketable securities:

Marketable securities are investments with original maturities exceeding three months, and have remaining maturities within twelve months. Marketable securities accrue interest based on a fixed interest rate for the term. The carrying value of marketable securities is recorded at cost plus accrued interest, which approximates their fair value.

(d) Intellectual Property

The costs incurred in establishing and maintaining patents for intellectual property developed internally are expensed in the period incurred.

(e) Property, plant and equipment:

Property, plant and equipment are stated at cost less accumulated depreciation and/or accumulated impairment losses, if any. Repairs and maintenance costs are expensed during the financial period in which they are incurred.

Property, plant and equipment are amortized over their estimated useful lives using the straight-line method based on the following rates:

Asset	Rate
Research equipment	5 years
Office furniture and equipment	5 years
Computer equipment	3 years
Leasehold improvements	Over the lesser of lease term or estimated useful life

(f) Impairment of long-lived assets:

The Company monitors its long-lived assets for indicators of impairment. If such indicators are present, the Company assesses the recoverability of affected assets by determining whether the carrying value of such assets is less than the sum of the undiscounted future cash flows of the assets. If such assets are found not to be recoverable, the Company measures the amount of such impairment by comparing the carrying value of the assets to the fair value of the assets, with the fair value generally determined based on the present value of the expected future cash flows associated with the assets. No impairment of long-lived assets was noted during the years ended December 31, 2015 and 2014.

(g) Concentration of credit risk and of significant customers:

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash and cash equivalents. Cash and cash equivalents were held at two major financial institutions in Canada. Such deposits may be in excess of insured limits in the event of non-performance by the institutions; however, the Company does not anticipate non-performance.

Collaborators whose collaboration research and development revenue accounted for 10% or more of total revenues were as follows:

	Year ended December 31,		
	2015	2014	2013
Genentech	\$4,563	\$15,764	\$12,876
Teva	11,010	12,588	13,773



(h) Financial instruments and fair value:

We measure certain financial instruments and other items at fair value.

To determine the fair value, we use the fair value hierarchy for inputs used to measure fair value of financial assets and liabilities. This hierarchy prioritizes the inputs to valuation techniques used to measure fair value into three levels: Level 1 (highest priority), Level 2, and Level 3 (lowest priority).

- Level 1 - Unadjusted quoted prices in active markets for identical instruments.
- Level 2 - Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly. Level 2 inputs include quoted prices for similar assets or liabilities in active markets, quoted prices for identical or similar assets or liabilities in markets that are not active, inputs other than quoted prices that are observable for the asset or liability (i.e., interest rates, yield curves, etc.), and inputs that are derived principally from or corroborated by observable market data by correlation or other means (market corroborated inputs).
- Level 3 - Inputs are unobservable and reflect the Company's assumptions as to what market participants would use in pricing the asset or liability. The Company develops these inputs based on the best information available.

Assets and liabilities are classified based on the lowest level of input that is significant to the fair value measurements. Changes in the observability of valuation inputs may result in a reclassification of levels for certain securities within the fair value hierarchy.

The Company's Level 1 assets include cash and cash equivalents and marketable securities with quoted prices in active markets. The carrying amount of accounts receivables, accounts payable and accrued expenses approximates fair value due to the nature and short-term of those instruments.

(i) Revenue recognition:

The Company recognizes revenue when all of the following criteria are met: (i) persuasive evidence of an arrangement exists; (ii) delivery has occurred or services have been rendered; (iii) the Company's price to the collaborator is fixed or determinable; and (iv) collectability is reasonably assured.

The Company generates revenue primarily through collaboration agreements.

Under these collaboration agreements, the Company is eligible to receive non-refundable upfront payments, funding for research and development services, milestone payments, other contingent payments and royalties. In assessing the appropriate revenue recognition related to a collaboration agreement, the Company first determines whether an arrangement includes multiple elements, such as the delivery of intellectual property rights and research and development services. Revenues associated with multiple element arrangements are attributed to the various elements based on their relative fair values or are recognized as a single unit of accounting when relative fair values are not determinable.

Non-refundable upfront payments are recorded as deferred revenue on the balance sheet and are recognized as collaboration revenue over the estimated period of research performance that is consistent with the terms of the research and development obligations contained in the collaboration agreement. The Company periodically reviews the estimated period of performance based on the progress made under each arrangement.

The Company recognizes funding related to full-time equivalent staffing funded through collaboration agreements as revenue on a gross basis as it performs or delivers such related services in accordance with the agreement terms, provided that it will receive payment for such services upon standard payment terms.

The Company recognizes revenue contingent upon its achievement of a milestone in its entirety, in the period the milestone is achieved, only if the milestone meets certain criteria and is considered to be substantive. Payments



received upon the occurrence of milestones that are non-substantive are deferred and recognized as revenue over the estimated period of performance applicable to the associated collaborative agreement.

(j) Research and development costs:

Research and development costs are expensed in the period in which they are incurred.

Certain development activity costs, such as preclinical costs, manufacturing costs and clinical trial costs, are a component of research and development costs and include fees paid to contract research organizations, investigators and other vendors who conduct certain product development activities on behalf of the Company. The amount of expenses recognized in a period related to service agreements is based on estimates of the work performed using an accrual basis of accounting. These estimates are based on patient enrollment, services provided and goods delivered, contractual terms and experience with similar contracts. The Company monitors these factors and adjusts the estimates accordingly. Payments made to third parties under these arrangements in advance of the receipt of the related services are recorded as prepaid expenses until the services are rendered.

(k) Stock-based compensation:

The Company grants stock options to employees, directors, officers and consultants pursuant to a stock option plan described in note 7c.

Employee stock-based compensation expense is measured at the grant date, based on the estimated fair value of the award, and is recognized as an expense, net of estimated forfeitures, over the requisite service period with a corresponding increase in additional paid-in capital. Stock-based compensation expense is amortized on a straight-line basis over the requisite service period for the entire award, which is generally the vesting period of the award. Any consideration received on exercise of stock options is credited to share capital.

(l) Liability classified stock options:

The Company granted stock options with exercise prices denominated in Canadian dollars under its Amended and Restated Stock Option Plan to members of its board of directors and certain consultants prior to the IPO. Following the change in functional currency on January 1, 2015, described in (n) below, the options denominated in Canadian dollars that were granted to members of the Company's board of directors and certain consultants were subject to liability accounting with fair value calculated using the Black-Scholes option-pricing model.

In September 2015, the Company modified certain compensation arrangements to be denominated in Canadian dollars. Following this modification, the options denominated in Canadian dollars that were granted to members of the Company's board of directors and certain consultants met the criteria for equity classification with fair value at the modification date calculated using the Black-Scholes option-pricing model and reclassified to additional paid-in capital. The modified awards were accounted for as equity awards from the date of modification.

(m) Net income (loss) per common share:

Basic net income (loss) per common share is computed by dividing the net income (loss) attributable to common shareholders by the weighted-average number of common shares outstanding for the period. Diluted net income (loss) per common share is computed using the treasury stock method, adjusting net income (loss) attributable to common shareholders to reallocate undistributed earnings based on the potential impact of dilutive securities.

Prior to the Company's IPO, net income (loss) per share was calculated under the two-class method as the Company had outstanding shares that met the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common shareholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. All of the outstanding redeemable convertible preferred shares converted to common shares upon the consummation of the Company's IPO in November 2014 (note 7a).

As the Company reported a net loss attributable to common shareholders for the year ended December 31, 2015, all stock options were anti-dilutive and were excluded from the diluted weighted average shares outstanding for that

period. For the year ended December 31, 2014, stock options of 154,057 (December 31, 2013 - 42,592) were excluded from the calculation of net income per common share because their inclusion would be anti-dilutive.

(n) Foreign currency translation:

The Company's reporting currency is the U.S. dollar. The functional currency of the Company changed to U.S. dollars from Canadian dollars on January 1, 2015 based on management's analysis of the changes in the primary economic environment in which the Company operates. The Company's reporting currency did not change. The change in functional currency is accounted for prospectively from January 1, 2015 and prior year financial statements have not been restated for the change in functional currency.

For all relevant periods, foreign currency revenue and expense transactions were recorded using the exchange rates prevailing at the dates of the transactions.

For periods prior to January 1, 2015, the effects of exchange rate fluctuations on translating foreign currency monetary assets and liabilities into Canadian dollars were included in the statement of operations and comprehensive income (loss) as foreign exchange gain (loss). Revenue and expense transactions were translated into the U.S. dollar reporting currency at the balance sheet date at average exchange rates during the period, and assets and liabilities were translated at end of period exchange rates, except for equity transactions, which were translated at historical exchange rates. Translation gains and losses from the application of the U.S. dollar as the reporting currency while the Canadian dollar was the functional currency are included as part of the cumulative foreign currency translation adjustment, which is reported as a component of shareholders' equity under accumulated other comprehensive income (loss).

For periods commencing January 1, 2015, monetary assets and liabilities denominated in foreign currencies are translated into U.S. dollars using exchange rates in effect at the balance sheet date. Opening balances related to non-monetary assets and liabilities are based on prior period translated amounts, and nonmonetary assets and nonmonetary liabilities incurred after January 1, 2015 are translated at the approximate exchange rate prevailing at the date of the transaction. Revenue and expense transactions are translated at the approximate exchange rate in effect at the time of the transaction. Foreign exchange gains and losses are included in the statement of operations and comprehensive income (loss) as foreign exchange gain (loss).

(o) Income taxes:

Deferred income taxes are recognized for the future tax consequences attributable to differences between the carrying amounts of assets and liabilities and their respective tax bases and net operating loss and credit carryforwards. Deferred income tax assets and liabilities are measured at enacted rates expected to apply to taxable income in the years in which those temporary differences and carryforwards are expected to be recovered or settled. The effect on deferred income tax assets and liabilities of a change in tax rates is recognized in the statement of operations and comprehensive income (loss) in the period that includes the enactment date. A valuation allowance is recorded when it is not more likely than not that all, or a portion of deferred income tax assets will be realized.

(p) Deferred tenant inducements:

Deferred tenant inducements, which include leasehold improvements paid for by the landlord and free rent, are recorded as liabilities on the balance sheet and recognized as a reduction of rent expense on a straight-line basis over the term of the lease.

(q) Segment and geographic information:

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment.

4. Future changes in accounting policies:

In May 2014, the Financial Accounting Standards Board ("FASB") issued amendments to clarify the principles of recognizing revenue and to develop a common revenue standard that would remove inconsistencies in revenue requirements, leading to improved comparability of revenue recognition practices across entities and industries. The amendments stipulate that an entity should recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to be entitled in exchange for those goods or services. Additional disclosure will also be required about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts, including significant judgments and changes in judgments, and assets recognized from costs incurred to obtain or fulfill a contract. In August 2015, the FASB issued an update

deferring the effective date of the new revenue standard by one year. The new guidance will be effective for public entities for fiscal years beginning after December 15, 2017 instead of the originally contemplated effective date of December 15, 2016. The Company is currently evaluating the new guidance to determine the impact it will have on the Company's financial position, results of operations and cash flows.

In August 2014, the FASB issued amendments requiring management to assess an entity's ability to continue as a going concern. For each reporting period, management will be required to evaluate whether there are conditions or events that raise substantial doubt about a company's ability to continue as a going concern within one year from the date the financial statements are issued. These amendments will be effective for public entities for the annual period ending after December 15, 2016, and for annual periods and interim periods thereafter. The adoption of these amendments in fiscal 2017 is not expected to have a material impact on the Company's financial statements.

## 5. Property, plant and equipment:

Property, plant and equipment consisted of the following:

	December 31,	
	2015	2014
Research equipment	\$6,925	\$6,815
Office furniture and equipment	1,040	980
Computer equipment	2,236	1,887
Leasehold improvements	6,370	6,338
Less: accumulated depreciation and amortization	(14,582)	(13,544)
Net book value	\$1,989	\$2,476

## 6. Accounts payable and accrued expenses:

Accounts payable and accrued expenses consisted of the following:

	December 31,	
	2015	2014
Trade payables	\$1,088	\$553
Employee compensation, benefits, and related accruals	762	1,077
Consulting and contracted research	506	774
Professional fees	214	180
Other	55	80
Total	\$2,625	\$2,664

## 7. Share capital:

## (a) Financing:

On November 10, 2014, the Company completed an IPO of 4,600,000 of its common shares at a purchase price of \$9.00 per share. On November 10, 2014, the Company also completed a private placement, in which the Company issued 495,000 of its common shares to an affiliate of Genentech at a price of \$9.00 per share. The Company received \$38.5 million of proceeds, net of underwriting discounts and commissions but before offering expenses, from the IPO and \$4.1 million of proceeds, net of underwriters' fees but before offering expenses, from the concurrent private placement.

Immediately prior to the closing of the IPO, all outstanding Series A and B redeemable convertible preferred shares were converted into common shares on a 1:1 basis and Series E redeemable convertible preferred shares were converted into common shares on a 1:1.2 basis, subject to certain adjustments. These adjustments differed for some of the Company's outstanding Series E preferred shares depending on the date of issue, resulting in different conversion ratios for different Series E preferred shares. All outstanding convertible preferred shares were converted into 7,725,924 common shares and 10,201 outstanding subscription rights were converted into 10,201 common shares.

Following the IPO, there were no preferred shares or subscription rights outstanding.

(b) Authorized share capital:

Prior to the IPO, the Company had authorized 1,205,761 Series A preferred shares, 1,028,806 Series B preferred shares, 4,620 Series C preferred shares, 9,376 Series D preferred shares and 4,370,920 Series E preferred shares. Holders of Series A, Series B and Series E preferred shares were entitled to receive non-cumulative cash dividends, in preference to any dividend payable on the common shares, at a rate of 8% per annum of the issue price of the preferred share when and as declared by the Board, but only if any dividends were declared on the common shares. In addition, holders of the Series A, Series B and Series E preferred shares would have been entitled to receive, when and as declared by the Board, dividends in an amount equal to any dividend per common share declared by the Board on the common shares multiplied by the number of common shares that would have been issued in exchange for the Series A, Series B and Series E preferred shares upon conversion. No dividends were declared prior to the conversion of the Series A, Series B and Series E preferred shares into common shares in connection with the closing of the IPO.

Immediately prior to the closing of the Company's IPO, the Company's articles were amended to remove all references to Series A, B, C, D and E preferred shares. As of December 31, 2014, no Series A, B, C, D or E convertible preferred shares were outstanding.

Post IPO, the Company's authorized share capital consists of an unlimited number of common and preferred shares without par value.

(c) Stock based compensation:

The Company's 2014 Equity Incentive Plan (the "2014 Plan") permits the grant of stock-based compensation awards to directors, officers, employees and consultants of the Company. The Company's pre-existing stock option plan (the "Amended and Restated Stock Option Plan") was limited to the granting of stock options as equity incentive awards whereas the 2014 Plan also allows for the issuance of restricted shares, restricted share units, share appreciation rights and performance shares. The 2014 Plan replaced the Amended and Restated Stock Option Plan. No further options will be granted under the Company's Amended and Restated Stock Option Plan.

The Amended and Restated Stock Option Plan provided for the grant of options for the purchase of common shares to directors, officers, employees and consultants prior to the Company's IPO. The options granted under the Amended and Restated Stock Option Plan vest on a graduated basis over a four-year period or less and each option's maximum term is ten years. The Amended and Restated Stock Option Plan will continue to govern the options granted thereunder.

Under the 2014 Plan, options granted generally vest on a graduated basis over a four-year period or less. The exercise price of the options is determined by the Board but must at least be equal to the fair market value of the common shares on the date of grant. Options may be exercised over a maximum term of ten years. As of December 31, 2015, a total of 4,742 stock options remain to be granted under the 2014 Plan. The number of common shares available for issuance under the 2014 Plan was increased by 375,000 in January 2016 as approved by the Board in accordance with the terms of the 2014 Plan.

Summary of stock option activity is as follows:

	Number of Options	Weighted Average Exercise Price CAD \$	U.S. \$	Aggregate Intrinsic Value
Outstanding, January 1, 2013	1,128,437	4.13	4.17	
Granted	292,418	3.74	3.64	
Exercised	(8,329 )	6.07	5.88	37
Forfeited, cancelled or expired	(79,427 )	4.90	4.76	
Outstanding, December 31, 2013	1,333,099	3.98	3.88	8,300
Granted	205,170	10.84	9.35	
Exercised	(2,417 )	6.07	5.23	23
Forfeited, cancelled or expired	(51,634 )	5.96	5.14	
Outstanding, December 31, 2014	1,484,218	4.88	4.20	15,551
Granted	529,288	18.73	14.67	
Exercised <sup>(1)</sup>	(270,254 )	4.66	3.65	2,426
Forfeited, cancelled or expired	(21,780 )	11.21	8.78	
Outstanding, December 31, 2015	1,721,472	9.62	6.95	1,880
Exercisable, December 31, 2015	1,034,576	4.42	3.20	5,010

(1) During the year ended December 31, 2015, 70,438 stock options were exercised for the same number of common shares in exchange for cash. In the same period, the Company issued 133,565 common shares for the cashless exercise of 199,816 stock options.





The following table summarizes the stock options outstanding and exercisable at December 31, 2015:

Range of Exercise Prices	Options Outstanding			Options Exercisable			
	Number of Remaining Options	Average Contractual Life (years)	Weighted Average Exercise Price	Number of Options Exercisable	Weighted Average Exercise Price		
	Outstanding		CAD \$	U.S. \$		CAD \$	U.S. \$
\$1.93 - \$2.31	236,759	5.70	2.67	1.93	181,768	2.67	1.93
\$2.32 - \$4.86	728,895	3.51	3.74	2.70	728,416	3.74	2.70
\$4.87 - \$7.72	179,842	9.41	10.43	7.54	25,732	9.76	7.05
\$7.73 - \$7.91	150,173	7.17	10.78	7.79	81,949	10.78	7.79
\$7.92 - \$17.70	86,533	8.77	15.69	11.34	16,598	13.87	10.02
\$17.71 - \$18.23	338,200	8.60	24.58	17.76	—	24.58	17.76
\$18.24 - \$21.82	1,070	9.11	27.58	19.92	113	30.20	21.82
	1,721,472	6.01	9.62	6.95	1,034,576	4.42	3.20

At December 31, 2015, there were 1,034,576 options exercisable with a weighted average remaining contractual life as at December 31, 2015 of 4.32 years.

A summary of the Company's non-vested stock option activity and related information for the year ended December 31, 2015 is as follows:

	Number of Options	Weighted Average Grant Date Fair Value
		CAD \$
		USD \$
Non-vested, January 1, 2015	367,654	5.64
Granted	529,288	12.55
Vested	(190,477)	6.72
Forfeited and cancelled	(19,569)	7.90
Non-vested, December 31, 2015	686,896	10.60

The aggregate fair value of options vested during the year ended December 31, 2015 was \$999 (2014 - \$722, 2013 - \$374).

The fair value of stock options at the date of grant is estimated using the Black-Scholes option-pricing model which requires multiple subjective inputs. The risk-free interest rate of the options is based on the U.S. Treasury yield curve in effect at the date of grant for a term similar to the expected term of the option. Prior to the IPO, the Company's stock

did not have a readily available market; therefore, the Company lacks company-specific historical and implied volatility information. Consequently, the expected volatility of stock options was estimated based on a historical volatility analysis of peers that were similar to the Company with respect to industry, stage of life cycle, size, and financial leverage. The expected term of the Company’s stock options has been determined utilizing the “simplified” method. Under this method, the expected term represents the average of the vesting period and the contractual term. The dividend yield is based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends. Forfeitures have been estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ materially from these estimates.

The weighted-average option pricing assumptions are as follows:

	Years ended December		
	2015	2014	2013
Average risk-free interest rate	1.75%	1.94%	1.03%
Expected volatility	75 %	73 %	70 %
Average expected term (in years)	6.23	6.13	6.20
Expected dividend yield	0.00%	0.00%	0.00%
Weighted average fair value of options granted	\$9.83	\$6.10	\$4.13

Stock-based compensation expense is classified in the statements of operations and comprehensive income (loss) as follows:

	Years ended December 31,		
	2015	2014	2013
Research and development	\$624	\$194	\$147
General and administrative	3,105	566	428
	\$3,729	\$760	\$575

As of December 31, 2015, the unrecognized stock-based compensation cost related to the non-vested stock options was \$4,650, which is expected to be recognized over a weighted-average period of 3.0 years.

#### 8. Foreign currency risk:

At December 31, 2015, the Company had U.S. dollar denominated cash and cash equivalents of \$17,836 (December 31, 2014 - \$46,531) and Canadian denominated cash and cash equivalents and marketable securities of CAD\$56,491 (December 31, 2014 - CAD\$43,516).

The Company faces foreign currency exchange rate risk in part, as a result of entering into transactions denominated in currencies other than U.S. dollars, particularly those denominated in Canadian dollars. The Company also holds non-U.S. dollar denominated cash and cash equivalents, marketable securities, accounts receivable and accounts payable, which are denominated in Canadian dollars.

Changes in foreign currency exchange rates can create significant foreign exchange gains or losses to the Company. The Company's current foreign currency risk is with the Canadian dollar, as a majority of non-U.S. dollar denominated expenses are denominated in Canadian dollars and the majority of cash and cash equivalents and marketable securities are held in Canadian dollars. To limit the Company's exposure to volatility in currency markets, management estimates anticipated expenses that will be denominated in Canadian and U.S. dollars and then purchases a corresponding amount of Canadian or U.S. dollars at the current spot rate. Once these estimated expense amounts are acquired, the Company does not hedge its exposure and thus assumes the risk of future gains or losses on the amounts of Canadian dollars held.

#### 9. Collaboration agreements:

The Company has entered into a number of collaboration agreements with multiple deliverables under which it may have received non-refundable upfront payments. The Company generally recognizes revenue from non-refundable upfront payments ratably over the term of its estimated period of performance of research under its collaboration

agreements in the event that such arrangements represent a single unit of accounting.

The collaborations may also include contractual milestone payments, which relate to the achievement of pre-specified research, development, regulatory and commercialization events. The milestone events coincide with the progression of product candidates from research and development, to regulatory approval and through to commercialization. The process of successfully discovering a new product candidate, having it selected by the collaborator for development and having it approved and ultimately sold for a profit is highly uncertain. As such, the milestone payments that the Company may earn from its collaborators involve a significant degree of risk to achieve.

Research and development milestones in the Company's collaboration agreements may include the following types of events:

- completion of preclinical research and development work leading to selection of product candidates;
- initiation of Phase 1, Phase 2 or Phase 3 clinical trials; and
- achievement of certain other scientific or development events.

Regulatory milestone payments may include the following types of events:

- filing of regulatory applications for marketing approval in the U.S., Europe or Japan, including investigational new drug ("IND") applications and new drug applications ("NDA"); and
- marketing approval in a major market, such as the U.S., Europe or Japan.

Commercialization milestone payments may include payments triggered by annual product sales that achieve pre-specified thresholds.

(a) uniQure Biopharma B.V. (“uniQure”) sublicense and research agreement:

Effective August 2000, the Company entered into a sublicense and research agreement with uniQure (formerly Amsterdam Molecular Therapeutics), pursuant to which the Company granted to uniQure an exclusive, worldwide sublicense under certain intellectual property controlled by the Company to develop and commercialize technology and compounds related to a certain variant of lipoprotein lipase (“LPL”). Under its sublicense and research agreement with uniQure, the Company collaborated with uniQure and the University of British Columbia (“UBC”) on preclinical activities, and thereafter uniQure developed an LPL gene therapy product, Glybera, which contains the LPL variant. Glybera was approved in the European Union (“EU”) in October 2012 to treat lipoprotein lipase deficiency (“LPLD”) in patients with severe or multiple pancreatitis attacks, despite dietary fat restrictions. uniQure conducted the clinical trials and is responsible for the commercialization of Glybera. During the year ended December 31, 2013, the Company received milestone payments of CAD\$547. No such milestone payments have been recognized in the years ended December 31, 2015 and 2014.

Under the terms of the agreement, the Company is eligible to receive certain additional milestone payments of less than CAD\$1,000 for Glybera and for each subsequent product, if any, developed pursuant to the agreement with uniQure. The Company, in turn, has certain payment obligations to its licensor, UBC, based on amounts received from uniQure or otherwise based on the exploitation of the licensed intellectual property. The Company believes that all potential milestone payments under this agreement are substantive and at risk at the inception of this agreement, and, as such, expects that future milestone payments will be recognized as revenue in the period that each milestone is achieved.

The Company is also eligible to receive mid single-digit royalties on net sales of the licensed products, for sales made by uniQure and its affiliates. The royalty rates for sales made by uniQure and its affiliates are reduced to a low single-digit when the licensed patents expire.

In July 2013, uniQure announced that it entered into a partnership with Chiesi Farmaceutici S.p.A. (“Chiesi”) for the commercialization of Glybera in the EU and more than a dozen other countries including Brazil, China, Mexico and Russia. With respect to uniQure’s sublicense to Chiesi, the Company is eligible to receive a percentage in the low twenties of all non-royalty compensation relating to the licensed technology or products that uniQure receives from Chiesi (including, for example, upfront payments and milestone payments), a percentage in the low twenties of any royalties that uniQure receives from Chiesi based on sales of technology or products covered by the licensed patents, plus a mid single-digit percentage of certain further royalties that uniQure receives from Chiesi based on sales of the Company’s licensed technology or products after the expiration of all licensed patents covering the product. If uniQure grants a sublicense to a third party other than to Chiesi, then the Company is eligible to receive a percentage in the low twenties of all non-royalty compensation relating to the licensed technology or products that uniQure receives from such sublicensee (for example, upfront payments and milestone payments) plus a percentage in the low twenties of any royalties that uniQure receives from such sublicensee based on sales of technology or products covered by the licensed patents. Royalties the Company is eligible to receive pursuant to its agreement with uniQure, including royalties related to sales made by Chiesi, are subject to customary royalty stacking deductions in the event that uniQure, or any of its sublicensees, have to license other technologies in order to commercialize Glybera.

Pursuant to the terms of the Company’s agreement with UBC, the Company must pay to UBC a single-digit percentage of amounts the Company receives from sales of Glybera.

(b) Teva Pharmaceutical Industries Ltd. (“Teva”) collaborative development and license agreement:

In December 2012, the Company entered into a collaborative development and license agreement with Teva, through its subsidiary, Ivax International GmbH, pursuant to which the Company granted Teva an exclusive worldwide license to develop and commercialize certain products, including TV-45070 (formerly XEN402).

Under the terms of the agreement, Teva paid the Company an upfront fee of \$41,000. The Company is collaborating with Teva to further develop TV-45070, and Teva is funding all development costs with respect to the licensed products. Teva is providing funding to the Company for certain of the Company's full-time equivalents ("FTEs") performing the research collaboration plan. The Company identified several deliverables under the agreement with Teva, including exclusive licenses to compounds and non-exclusive licenses to companion diagnostic products, a commitment to participate in a joint steering committee and research and development services to be performed by the Company on behalf of Teva. The Company concluded that the licenses did not have stand-alone value to Teva without the Company's technical expertise and joint steering committee participation during the initial three-year period.

Therefore, the Company has determined that the various deliverables under this agreement should be considered as one single unit of accounting. As such the Company determined that the \$41,000 upfront payment should be recognized as revenue ratably over the expected period of performance, being the three-year period ended December 31, 2015.

In addition, the Company is eligible to receive potential milestone payments totaling up to \$335,000, comprised of a \$20,000 clinical milestone payment, up to \$285,000 in regulatory milestone payments, and a \$30,000 sales-based milestone payment. If TV-45070 is approved, the Company is also eligible to receive royalties in the low teens to low twenties on net sales of licensed products for the timeframe that such products are covered by the licensed patents and in certain other instances. The Company believes that potential milestone payments for development and regulatory milestones under this agreement are substantive and at risk at the inception of this agreement, and, as such, expects that these future milestone payments will be recognized as revenue in the period that each milestone is achieved. The Company believes that the potential sales-based milestone payments under this agreement are not substantive as the Company does not expect to contribute effort to their achievement and expects such sales-based milestones will generally be achieved after the period of substantial involvement under the collaboration. Therefore, the Company expects that future sales-based contingent consideration milestone payments will be recognized as revenue when such milestones are achieved, assuming all other revenue recognition criteria are met. To date, no such milestone payments have been recognized.

Pursuant to the terms of the Company's agreement with the Memorial University of Newfoundland, the Company must pay to the Memorial University of Newfoundland certain milestone payments, a single-digit percentage of net sales for pain products the Company sells directly and a single-digit percentage of royalties received for sales of pain products by the Company's third party licensees, such as under the Teva and Genentech agreements.

(c) Genentech collaborative research and license agreement:

In December 2011, the Company entered into a collaborative research and license agreement with Genentech and its affiliate, F. Hoffman-La Roche Ltd. ("Roche") to discover and develop small and large molecules that selectively inhibit the Nav1.7 sodium channel and companion diagnostics for the potential treatment of pain. Pursuant to this agreement, the Company granted Genentech a worldwide exclusive license to develop and commercialize compounds directed to Nav1.7 and products incorporating such compounds for all uses. The Company also granted Genentech a worldwide non-exclusive license to diagnostic products for the purpose of developing or commercializing such compounds.

Under the terms of the agreement, Genentech paid the Company an upfront fee of \$10,000. Genentech is providing funding to the Company for certain of the Company's FTEs performing the research collaboration plan. The Company identified several deliverables under the agreement with Genentech, including exclusive licenses to compounds and non-exclusive licenses to diagnostic products, a commitment to participate in a joint steering committee and research and development services to be performed by the Company on behalf of Genentech. The Company concluded that the licenses did not have stand-alone value to Genentech without the Company's technical expertise and joint steering committee participation during the initial three year period. Therefore, the Company has determined that the various deliverables should be considered as a single unit of accounting. As such the Company determined that the \$10,000 upfront payment should be recognized as revenue ratably over the expected period of performance, being the three-year period ended December 22, 2014.

The Company is eligible to receive pre-commercial and commercial milestone payments with respect to the licensed products totaling up to an additional \$613,000, comprised of up to \$45,500 in preclinical and clinical milestone payments, up to \$387,500 in regulatory milestone payments, and up to \$180,000 in sales-based milestone payments for multiple products and indications. In addition, the Company is eligible to receive royalties based on net sales of the licensed products, which range from a mid single-digit percentage to ten percent for small-molecule inhibitors for the timeframe that such products are covered by the licensed patents and a low single-digit percentage thereafter until the date that is ten years after first commercial sale on a country-by-country basis, plus a low single-digit percentage for large-molecule inhibitors of Nav1.7 for a period of ten years from first commercial sale on a country-by-country basis. The Company believes that the potential milestone payments for preclinical, clinical and regulatory milestones under this agreement are substantive and at risk at inception of this agreement, and, as such, expects that these future milestone payments will be recognized as revenue in the period that each milestone is achieved. In the year ended



December 31, 2015, no milestone payments have been recognized (2014 - \$8,000; 2013 - \$5,000).

The Company believes that the potential sales-based milestone payments under this agreement are not substantive as the Company does not expect to contribute effort to their achievement and expects such sales-based milestones will generally be achieved after the period of substantial involvement under the collaboration. Therefore, the Company expects that future sales-based contingent consideration milestone payments will be recognized as revenue when such milestones are achieved, assuming all other revenue recognition criteria are met. To date, no such milestone payments have been recognized.

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In March 2014, the Company entered into a new agreement with Genentech for pain genetics, using the Company's Extreme Genetics discovery platform to focus on identifying genetic targets associated with rare phenotypes where individuals have an inability to perceive pain or where individuals have non-precipitated spontaneous severe pain. Pursuant to the terms of this agreement, any intellectual property arising out of the collaboration will be jointly owned by the Company and Genentech. The Company also granted Genentech a time-limited, exclusive right of first negotiation on a target-by-target basis to form joint drug discovery collaborations. Under the terms of this agreement, Genentech paid an upfront payment of \$1,500. The Company is eligible to receive additional milestone payments totaling up to \$1,750. At the option of the Company, a Genentech affiliate invested \$4,455 in a private placement concurrent with the IPO (note 7a).

The Company identified several deliverables under this agreement with Genentech, including non-exclusive licenses to certain intellectual property controlled by the Company, a commitment to participate in a joint steering committee and collaborative research services to be performed by the Company. The Company concluded that the licenses did not have stand-alone value to Genentech without the Company's technical expertise and joint steering committee participation during the initial two year period. Therefore, the Company has determined that the various deliverables should be considered as a single unit of accounting. As such the Company determined that the \$1,500 upfront payment should be recognized as revenue ratably over the expected period of performance, being the two-year period ending March 18, 2016.

The Company believes that the potential milestone payments under this agreement are substantive and at risk at inception of this agreement, and, as such, expects that these future milestone payments will be recognized as revenue in the period that each milestone is achieved. In the year ended December 31, 2015, a \$250 milestone payment has been recognized (2014 - nil).

(d) Ionis Pharmaceuticals, Inc. ("Ionis") collaboration and licensing agreement:

In November 2010, the Company entered into a collaboration and license agreement with Ionis (formerly Isis Pharmaceuticals, Inc.). The Company issued Ionis a convertible, interest bearing promissory note as payment of the \$1,500 upfront fee required by the agreement, which was accounted for as a research and development expense. During 2013, the Company made this payment to Ionis, including accrued interest, pursuant to the terms of the convertible promissory note.

Under the terms of this agreement, the Company received an option to obtain from Ionis worldwide exclusive licenses to develop and commercialize antisense products targeting hepcidin and/or hemojuvelin, each of which is a validated target for anemia of chronic disease, which the Company exercised in 2013. The Company paid Ionis an option exercise fee of \$2,000, which was accounted for as a research and development expense for the period. In late 2013, the Company discontinued development of product candidates under this program and in 2014, the Company terminated its agreement with Ionis.

(e) Genome BC collaboration agreement:

In January 2009, the Company entered into a research funding agreement with Genome BC to co-fund IND-enabling studies for antisense products targeting hepcidin or hemojuvelin. The deliverables of the research activities are to identify development candidates for both hepcidin and hemojuvelin targets. Under the agreement with Genome BC, the Company carried out certain research activities with partial funding that Genome BC provided on a quarterly basis over the term of the research program. This agreement expired at the end of its term on September 30, 2013.

The following table is a summary of the revenue recognized from the Company's collaborations for each of the years ended December 31, 2015, 2014 and 2013.

	Year Ended December 31,		
	2015	2014	2013
<b>uniQure:</b>			
Milestone payment	\$—	\$14	\$531
<b>Teva:</b>			
Recognition of upfront payment	10,897	12,255	13,143
Research funding	112	333	630
<b>Genentech:</b>			
Recognition of upfront payment	725	3,603	3,300
Research funding	3,589	4,248	4,514
Milestone payment	250	7,913	5,062
<b>Genome BC:</b>			
Research funding	—	—	172
Total collaboration revenue	\$15,573	\$28,366	\$27,352

#### 10. Commitments and contingencies:

##### (a) Lease commitments:

The Company entered into an amended lease agreement for research laboratories and office space in Burnaby, British Columbia, Canada for a 120-month term from April 1, 2012 to March 31, 2022, which included an element of free rent and tenant inducement that will be amortized over the term of the lease.

Lease expense for the year ended December 31, 2015 was \$917 (2014 - \$915, 2013 - \$962). Future minimum annual lease payments under existing operating lease commitments are as follows:

Year ending December 31:	
2016	972
2017	1,071
2018	1,091
2019	1,093
2020	1,094
2021 and thereafter	1,273
Total	\$6,594

##### (b) Priority access agreement with Medpace:

In August 2015, the Company entered into a priority access agreement with Medpace for the provision of certain clinical development services. Under the terms of the agreement, the Company has committed to using Medpace non-exclusively for clinical development services over the five year term of the agreement. In consideration for priority access to Medpace resources and preferred service rates, the Company has committed to \$7,000 of services

over the term of the agreement, \$3,000 of which was paid in the year ended December 31, 2015. Of the amounts paid by the Company in 2015 in connection with the priority access agreement, \$896 has been recorded as expenses for services rendered during the year ended December 31, 2015, \$1,010 has been recorded as current prepaid expenses and \$1,094 as long-term prepaid expenses for the provision of future services as at December 31, 2015.

(c) Guarantees and indemnifications:

The Company has entered into license and research agreements with third parties that include indemnification provisions that are customary in the industry. These indemnification provisions generally require the Company to compensate the other party for certain damages and costs incurred as a result of third party claims or damages arising from these transactions.

The maximum amount of potential future indemnification is unlimited; however, the Company currently holds commercial and product liability insurance. This insurance limits the Company's exposure and may enable it to recover a portion of any future amounts paid. Historically, the Company has not made any indemnification payments under such agreements and the Company believes that the fair value of these indemnification obligations is minimal. Accordingly, the Company has not recognized any liabilities relating to these obligations for any period presented.

## 11. Income taxes:

Income tax (recovery) expense varies from the amounts that would be computed by applying the expected Canadian and provincial statutory income tax rate of 26% (2014 – 26%, 2013- 25.75%) to loss before income taxes as shown in the following table:

	2015	2014	2013
Computed taxes (recoveries) at Canadian federal and provincial tax rates	\$(4,095)	\$3,385	\$3,098
Tax attributes expired/utilized	2,851	2,011	198
Change in valuation allowance	2,482	(2,364)	(2,029)
Investment tax credits earned	(1,220)	(1,283)	(529 )
Non-deductible expenditures	977	(1,053)	(374 )
Changes in tax rates	—	—	(1,019)
Financing fees in equity	—	(1,945)	—
Other	(995 )	1,249	655
Income tax (recovery) expense	\$—	\$—	\$—

Deferred income tax assets and liabilities result from the temporary differences between the amount of assets and liabilities recognized for financial statement and income tax purposes. The significant components of the Company's net deferred income tax assets are as follows:

	2015	2014
Deferred income tax assets		
Investment tax credits	\$21,303	\$20,108
Scientific research and experimental development pool	21,088	19,648
Non-capital losses	4,234	1,390
Depreciable assets	3,749	2,651
Deferred financing fees	959	1,318
Deferred revenues	41	3,063
Other	144	858
Less - valuation allowance	(51,518)	(49,036)
Net deferred income tax assets	\$—	\$—

The realization of deferred income tax assets is dependent upon the generation of sufficient taxable income during future periods in which the temporary differences are expected to reverse. The valuation allowance is reviewed on a quarterly basis and if the assessment of the “more likely than not” criteria changes, the valuation allowance is adjusted accordingly. A full valuation allowance continues to be applied against deferred income tax assets as the Company has assessed that the realization of such assets does not meet the “more likely than not” criteria.

At December 31, 2015, the Company has unclaimed tax deductions for scientific research and experimental development expenditures of \$81,107 (2014 - \$75,571) with no expiry.

At December 31, 2015, the Company has \$18,875 (2014 - \$17,942) of investment tax credits available to offset federal taxes payable and \$7,385 (2014 - \$6,891) of provincial tax credits available to offset provincial taxes payable in the future.

At December 31, 2015, the Company has non-capital losses, net of uncertain tax positions, carried forward for tax purposes, which are available to reduce taxable income of future years of approximately \$16,285 (2014 - \$5,347).

The investment tax credits and loss carry forwards expire over various years to 2035.

As of December 31, 2015, the total amount of the Company's unrecognized tax benefits were \$6,350 (2014 - \$6,350). If recognized in future periods, the unrecognized tax benefits would affect our effective tax rate. The Company recognizes potential accrued interest and penalties related to unrecognized tax benefits within the income tax provision. Interest and penalties have not been accrued at December 31, 2015 as none would be owing on the unrecognized tax benefits due to the availability of non-capital losses to shelter any potential taxable income arising thereon.

The Company does not currently expect any significant increases or decreases to these unrecognized tax benefits within 12 months of the reporting date.

The Company currently files an income tax return in Canada, the jurisdiction in which it is subject to tax. In jurisdictions in which the Company does not believe it is subject to tax and therefore does not file income tax returns, the Company can provide no certainty that tax authorities in those jurisdictions will not subject one or more tax years (since the inception of the Company) to examination. Further, while the statute of limitations in each jurisdiction where an income tax return has been filed generally limits the examination period, as a result of loss carry-forwards, the limitation period for examination generally does not expire until several years after the loss carry-forwards are utilized. Other than routine audits by tax authorities for tax credits and tax refunds that the Company claims, the Company is not aware of any other material income tax examination currently in progress by any taxing jurisdiction. Tax years ranging from 2002 to 2014 remain subject to Canadian income tax examinations.

#### 12. Related parties:

Dr. August J. Troendle, an officer and director of Medpace, which provides clinical development services to the Company, is a beneficial owner of more than 5% of the Company's common shares. The Company incurred \$922 of clinical development service fees under its priority access agreement and a master services agreement with Medpace for the year ended December 31, 2015 (2014 – nil, 2013 – nil). Additionally, the Company has recorded \$2,314 of prepaid expenses as of December 31, 2015 (December 31, 2014 - nil) for future clinical development services under such agreements with Medpace.

#### 13. Selected quarterly financial data (unaudited):

The following table presents certain unaudited quarterly financial information for the years ended December 31, 2015 and 2014 (in thousands of U.S. dollars except per share amounts). This information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods.

	Three Months Ended			
	March 31,	June 30,	September 30,	December 31,
	2015	2015	2015	2015
Revenue	\$4,010	\$4,046	\$ 4,294	\$ 3,227
Income (loss) from operations	(6,137)	199	(820 )	(2,603 )
Net income (loss) attributable to common shareholders	(9,156)	1,168	(3,827 )	(3,937 )
Basic net income (loss) per common share	\$(0.64 )	\$0.08	\$( 0.27 )	\$( 0.27 )
Diluted net loss per common share	\$(0.64 )	\$(0.07 )	\$( 0.27 )	\$( 0.27 )

  

	Three Months Ended			
	March 31,	June 30,	September 30,	December 31,

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	2014 <sup>(1)</sup>	2014 (1)	2014 <sup>(1)</sup>	2014
Revenue	\$5,001	\$5,298	\$ 13,193	\$ 4,878
Income from operations	1,032	1,378	8,661	35
Net income attributable to common shareholders	—	—	3,595	1,224
Basic net income per common share	\$—	\$—	\$ 2.67	\$ 0.14
Diluted net income per common share	\$—	\$—	\$ 1.69	\$ 0.13

(1) The financial data, including per share amounts, for all interim periods prior to and including the three month period ended September 30, 2014, do not reflect the IPO.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure  
None.

Item 9A. Controls and Procedures

Evaluation of disclosure controls and procedures. Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2015. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company’s management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure.



Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2015, our Chief Executive Officer and our Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were, in design and operation, effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting. Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer, is responsible for establishing and maintaining adequate internal control over our financial reporting, as such term is defined in Rule 13a-15(f) and Rule 15d-15(f) of the Securities Exchange Act of 1934. Our internal control over financial reporting is a process to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Our internal control over financial reporting includes those policies and procedures that:

- (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets;
- (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

The effectiveness of any system of internal control over financial reporting, including ours, is subject to inherent limitations, including the exercise of judgment in designing, implementing, operating, and evaluating the controls and procedures, and the inability to eliminate misconduct completely. Accordingly, any system of internal control over financial reporting, including ours, no matter how well designed and operated, can only provide reasonable, not absolute, assurances. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions or that the degree of compliance with the policies or procedures may deteriorate. Management has assessed the effectiveness of our internal control over financial reporting as at December 31, 2015. In making its assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control – Integrated Framework (2013) to evaluate the effectiveness of our internal control over financial reporting. Based on this assessment using those criteria, management has concluded that our internal control over financial reporting was effective as of December 31, 2015.

Changes in internal control over financial reporting. There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the three months ended December 31, 2015 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None



### PART III

#### Item 10. Directors, Executive Officers and Corporate Governance

The information required by Item 10 of Form 10-K is incorporated by reference to our Proxy Statement for the 2016 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2015.

#### Item 11. Executive Compensation

The information required by Item 11 of Form 10-K is incorporated by reference to our Proxy Statement for the 2016 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2015.

#### Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Shareholder Matters

The information required by Item 12 of Form 10-K is incorporated by reference to our Proxy Statement for the 2016 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2015.

#### Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by Item 13 of Form 10-K is incorporated by reference to our Proxy Statement for the 2016 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2015.

#### Item 14. Principal Accounting Fees and Services

The information required by Item 14 of Form 10-K is incorporated by reference to our Proxy Statement for the 2016 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2015.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Financial Statements — The financial statements included in Item 8 are filed as part of this Annual Report on Form 10-K.

(a)(2) Financial Statement Schedules — All schedules have been omitted because they are not applicable or required, or the information required to be set forth therein is included in the Financial Statements or notes thereto included in Item 8 of this Annual Report on Form 10-K.

(a)(3) Exhibits — The exhibits required by Item 601 of Regulation S-K are listed in paragraph (b) below.

(b) Exhibits — The exhibits listed on the Exhibit Index (following the Signatures section of this report) are filed herewith or are incorporated by reference to exhibits previously filed with the SEC.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Dated: March 8, 2016 XENON PHARMACEUTICALS INC.

By: /s/ Simon Pimstone  
Simon Pimstone  
President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose signature appears below hereby constitutes and appoints Simon Pimstone and Ian Mortimer, and each of them severally, as his true and lawful attorneys-in-fact and agents, with full power to act without the other and with full power of substitution and resubstitution, for him and in his name, place and stead, in any and all capacities (including his capacity as a director and/or officer of Xenon Pharmaceuticals Inc.) to sign any and all amendments and supplements to this report, and any and all other instruments necessary or incidental in connection herewith, and to file the same, with all exhibits thereto, and all other documents in connection therewith, with the Commission.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Simon Pimstone		March 8, 2016
Simon Pimstone	President, Chief Executive Officer and Director (Principal Executive Officer)	
/s/ Ian Mortimer		March 8, 2016
Ian Mortimer	Chief Financial Officer and Chief Operating Officer (Principal Financial and Accounting Officer)	
/s/ Michael Tarnow		March 8, 2016
Michael Tarnow	Chair of the Board of Directors	

/s/ Mohammad Azab		March 8, 2016
Mohammad Azab	Director	
/s/ Steven Gannon		March 8, 2016
Steven Gannon	Director	
/s/ Michael Hayden		March 8, 2016
Michael Hayden	Director	
/s/ Frank Holler		March 8, 2016
Frank Holler	Director	
/s/ Gary Patou		March 8, 2016
Gary Patou	Director	
/s/ Richard Scheller		March 8, 2016
Richard Scheller	Director	

## EXHIBIT INDEX

Exhibit Number	Description of Document	Incorporated by Reference			Filing Date
		Form	File No.	Exhibit	
3.1	Articles of the Company.	10-Q	001-36687	3.1	December 15, 2014
3.2	Amended and Restated By-laws of the Company.	10-Q	001-36687	3.2	December 15, 2014
4.1	Form of Common Share Certificate.	S-1/A	333-198666	4.1	October 6, 2014
4.2	Amended and Restated Investor Rights Agreement, dated December 6, 2006, by and among the Company and the investors listed on Exhibit A and Exhibit B thereto, as amended.	S-1/A	333-198666	4.2	October 6, 2014
10.1†	Exclusive Collaborative Research and Option Agreement, dated June 10, 2009, by and between the Company and Merck Sharp & Dohme Research Ltd, as amended.	S-1/A	333-198666	10.1	October 6, 2014
10.2†	Sublicense and Research Agreement, dated June 18, 2001, by and between the Company and uniQure Biopharma B.V. (formerly Amsterdam Molecular Therapeutics B.V.), as amended by the Consent of the Company and the University of British Columbia to the uniQure-Chiesi Agreement, dated June 28, 2013.	S-1/A	333-198666	10.2	October 6, 2014
10.3†	Collaborative Research and License Agreement, dated December 22, 2011, by and among the Company, Genentech, Inc. and F. Hoffmann-La Roche Ltd, as amended.	S-1/A	333-198666	10.3	October 6, 2014
10.4†	Collaborative Development and License Agreement, dated December 7, 2012, by and between the Company and Ivax International GmbH, as amended.	S-1/A	333-198666	10.4	October 6, 2014
10.5†	License Agreement, dated August 1, 2000, by and between the Company and the University of British Columbia, as amended.	S-1/A	333-198666	10.5	October 6, 2014
10.6	Consulting Agreement, dated January 1, 2004, by and between the Company and Genworks Inc., as amended.	S-1	333-198666	10.6	September 10, 2014
10.7#	Stock Option Plan, as amended, and form of option agreement thereunder.	S-1/A	333-198666	10.7	October 6, 2014
10.8#	2014 Equity Incentive Plan, and form of option agreement thereunder.	S-1	333-198666	10.8	September 10, 2014

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10.9#	Offer Letter, dated October 3, 2014, by and between the Company and Simon Pimstone.	S-1/A	333-198666	10.9	October 6, 2014
10.10#	Offer Letter, dated October 3, 2014, by and between the Company and Paul Goldberg.	S-1/A	333-198666	10.10	October 6, 2014
10.11#	Offer Letter, dated October 3, 2014, by and between the Company and Ian Mortimer.	S-1/A	333-198666	10.11	October 6, 2014
10.12#	Offer Letter, dated October 3, 2014, by and between the Company and Karen Corraini.	S-1/A	333-198666	10.12	October 6, 2014
10.13#	Offer Letter, dated October 3, 2014, by and between the Company and Robin Sherrington.	S-1/A	333-198666	10.13	October 6, 2014

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Exhibit Number	Description of Document	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
10.14	Lease, dated as of 2001, by and between the Company and Discovery Parks Incorporated, as amended through July 1, 2014.	S-1	333-198666	10.14	September 10, 2014
10.15#	Form of Director and Executive Officer Indemnification Agreement.	S-1/A	333-198666	10.15	October 6, 2014
10.16	Common Share Put Agreement, dated as of March 19, 2014, by and between the Company and Roche Finance LTD.	S-1	333-198666	10.16	September 10, 2014
10.17†	Amendment #4, dated May 13, 2015, to the Collaborative Research and License Agreement, dated December 22, 2011, by and among the Company, Genentech, Inc. and F. Hoffman-La Roche Ltd, as amended.	10-Q	001-36687	10.1	August 13, 2015
10.18	Lease Modification Agreement, effective July 1, 2015, by and between the Company and Redstone Enterprises Ltd.	10-Q	001-36687	10.1	November 10, 2015
10.19	Lease Modification Agreement, effective December 1, 2015, by and between the Company and Redstone Enterprises Ltd.				
10.20†	Amendment #5, dated November 19, 2015, to the Collaborative Research and License Agreement, dated December 22, 2011, by and among the Company, Genentech, Inc. and F. Hoffman-La Roche Ltd, as amended.				
21.1	List of Subsidiaries of the Company.	S-1	333-198666	21.1	September 10, 2014
23.1	Consent of KPMG LLP, Independent Registered Public Accounting Firm.				
24.1	Powers of Attorney (contained on signature page).				
31.1	Rule 13a-14(a) / 15d-14(a) Certification of Principal Executive Officer				
31.2	Rule 13a-14(a) / 15d-14(a) Certification of Principal Financial Officer				
32.1*	Section 1350 Certification of Principal Executive Officer				
32.2*	Section 1350 Certification of Principal Financial Officer				
101	The following financial statements from the Company's Annual Report on Form 10-K for the year ended December 31, 2015,				

formatted in XBRL: (i) Statements of Cash Flows, (ii) Statements of Operations and Comprehensive Income (Loss), (iii) Balance Sheets, and (iv) Notes to Financial Statements, tagged as blocks of text and including detailed tags.

€ Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

# Indicates management contract or compensatory plan.

\* The Certifications attached as Exhibits 32.1 and 32.2 that accompany this Annual Report on Form 10-K are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of Xenon Pharmaceuticals Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.