Xenon Pharmaceuticals Inc.
Form 10-K
March 12, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2014

or

¨TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number: 001-36687

XENON PHARMACEUTICALS INC.

(Exact Name of Registrant as Specified in its Charter)

Canada	98-0661854
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

200 – 3650 Gilmore Way

Burnaby, British Columbia V5G 4W8

Canada

(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 x

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 x

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 x 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 x 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 x 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 x

The aggregate market value of the voting and non-voting common shares held by non-affiliates of the registrant on November 5, 2014 (including common shares issued in the registrant's initial public offering), based on the closing price of $10.50 per share for the registrant's common shares as reported by The NASDAQ Global Market, was approximately $111 million. The registrant has elected to use November 5, 2014 as the calculation date, which was the initial trading date of the registrant's common shares on The NASDAQ Global Market, because on June 30, 2014 (the last business day of the registrant's most recently completed second fiscal quarter), the registrant was a privately-held company. Common shares held by each executive officer and director and by each person who owns 5% or more of the outstanding common shares, based on filings with the Securities and Exchange Commission, have been excluded from this computation since such persons may be deemed to be affiliates of the registrant. 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 9, 2015 was 14,221,600.

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 2015 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, 2014.

XENON PHARMACEUTICALS INC.

FORM 10-K

For the Fiscal Year Ended December 31, 2014

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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 expr 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 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 use of proceeds from our initial public offering and the concurrent private placement completed in November 2014;
- 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.

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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.

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 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. Our Extreme Genetics discovery platform has yielded the first approved gene therapy product in the European Union, or the EU, a broad development pipeline and multiple pharmaceutical partnerships. 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 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 $150.0 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.

To date, our Extreme Genetics discovery platform has yielded:

- 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. We believe that uniQure's commercialization partner, Chiesi Farmaceutici S.p.A., or Chiesi, plans to launch Glybera in the first quarter of 2015;
- TV-45070 (formerly XEN402), a product candidate with four Phase 2 proof-of-concept clinical trials completed. Our partner Teva is conducting a 300-patient, randomized Phase 2b clinical trial in osteoarthritis, or OA, of the knee, with data expected in the third quarter of 2015 and is planning a Phase 2b clinical trial in patients with postherpetic neuralgia, or PHN, with patient enrollment expected to begin in March 2015;
- GDC-0276, a product candidate being developed in collaboration with Genentech for the treatment of pain. In September 2014, Genentech initiated a Phase 1 clinical trial for GDC-0276. The Phase 1 clinical trial has recently been expanded and is expected to complete enrollment in the second half of 2015. GDC-0276 is a selective, oral Nav1.7 small-molecule inhibitor being developed for the treatment of pain; and

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proprietary preclinical programs including a sodium channel inhibitor for the orphan disorder Dravet Syndrome, or DS, and XEN801, a stearoyl Co-A desaturase, or SCD1, inhibitor for the treatment of acne. We anticipate filing an investigational new drug, or IND or IND equivalent application for XEN801 in the second quarter of 2015 and an IND for our DS program in 2016.

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.

A significant focus of our Extreme Genetics discovery platform has been human channelopathies. This focus has enabled us to develop strong capabilities in small-molecule ion channel drug discovery. Our ion channel discovery capability is based on our understanding of the genetics of channelopathies combined with our proprietary biology and medicinal chemistry assets and know-how. We have been able to discover new binding sites on ion channels which, in turn, has 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 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. The efficacy of non-selective ion channel inhibitors has generally been limited by the adverse events observed at high doses due to the broad non-selective binding of such agents. 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.

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 Dravet Syndrome. We believe that our Extreme Genetics discovery platform provides the opportunity to validate additional ion channel targets for both prevalent and orphan indications.

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.”

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.

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. 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.

Our Pipeline

The following is a summary of our current product pipeline:

Approved Product

Glybera

Glybera is the first and currently the only gene therapy product to receive commercial approval in the EU. It is specifically indicated for the treatment of a subset of adult patients with the orphan lipid disorder lipoprotein lipase deficiency, or LPLD, confirmed by genetic testing and suffering from 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. Together with collaborators from the University of British Columbia, or UBC, we demonstrated that humans with a single gene variant of the lipoprotein lipase, or LPL, gene called LPL^{S447X}, 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 an LPL gene therapy product, Glybera, which contains the LPL^{S447X} variant. We believe that the introduction of the therapeutic LPL^{S447X} gene through administration of Glybera provides a clinical benefit for a subset of LPLD patients.

Glybera is the first product whose active ingredient was derived from our platform to receive commercial approval. 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. Glybera was developed by our licensee, uniQure. In 2012, Glybera was approved in the EU, and in July 2013, uniQure announced that it had entered into a partnership with Chiesi Farmaceutici S.p.A., or Chiesi, for the commercialization of Glybera in the EU and more than a dozen other countries including Brazil, China, Mexico and Russia. We believe that Chiesi plans to launch Glybera in the first quarter of 2015 in Europe, and that uniQure is pursuing a U.S. product approval strategy, with plans to file a Biologics License Application, or BLA, with the U.S. Food and Drug Administration, or the FDA, following receipt of the results from a planned Phase 4 trial expected to begin in mid-2015. Glybera has received both fast track and orphan drug designations for the treatment of LPLD in both the EU and the U.S.

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. 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 product.

Product Candidates in Development

TV-45070 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 potentially broad application in nociceptive pain, mediated by damage or injury to tissues, including the pain sensitivity caused by inflammation, and neuropathic pain mediated by damage, dysfunction or injury of nerves. TV-45070 is partnered with Teva. Pursuant to the terms of the agreement, Teva is obligated to complete three Phase 2 or later stage clinical trials. Using a topical ointment formulation of TV-45070, Teva has initiated a 300-patient, randomized Phase 2b clinical trial in OA of the knee with data expected in the third quarter of 2015. Teva is also developing topical TV-45070 in neuropathic pain indications, and is planning a Phase 2b clinical trial in patients with PHN with patient enrollment expected to begin in March 2015. We selected Nav1.7 as a drug target after we discovered that the Nav1.7 protein is deficient in the rare human disease called congenital indifference to pain, or 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 International GmbH, or Ivax, pursuant to which we granted Teva an exclusive worldwide license to develop and commercialize TV-45070. Prior to our entry into the 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 OA (November 2013). Under the terms of the agreement, Teva made an upfront payment to us of $41.0 million. 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 that such products are covered by the licensed patents and in certain other instances. We also have an option to co-promote products in the U.S.

GDC-0276 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. Hoffmann-La Roche Ltd, or Roche, to discover and develop selective oral inhibitors of Nav1.7 for the treatment of pain. 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. The first small molecule, preclinical product candidate that was selected for development under our collaboration is GDC-0276. In September 2014, Genentech initiated a Phase 1 clinical trial for GDC-0276. The Phase 1 clinical trial has recently been expanded and is expected to complete enrollment in the second half of 2015. GDC-0276 is a selective, oral Nav1.7 small-molecule inhibitor being developed for the treatment of pain.

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. We are also 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 also 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, plus a low single-digit percentage for large-molecule inhibitors of Nav1.7.

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.

Product Candidates in Discovery

Selective Small-Molecule Sodium Channel Inhibitors for the Treatment of Dravet Syndrome

We are developing selective inhibitors of the voltage-gated sodium channel Nav1.6 as a treatment for the orphan disease Dravet Syndrome, or 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 DS.

DS is a severe form of childhood epilepsy that typically causes mental retardation and, in approximately 10% of cases, premature death before the age of 12 years. The frequency of DS in the U.S. has been estimated to be one in 20,000 to 40,000 births, which, when applied to U.S. federal census data, correlates to approximately 7,500 to 15,000 patients with DS in the U.S.

With our collaborators from McGill University, we identified the genetic link between rare human epilepsy and mutations in the Nav1.1 gene. 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 DS. To further support inhibiting Nav1.6 as a potential therapeutic approach to treat DS, published data have 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.

DS is one of the most resistant epilepsies to treatment. Some benefit has been reported for drugs that increase the activity of the inhibitory brain pathways such as benzodiazepines and Stiripentol, while non-selective sodium channel blockers such as lamotrigine are contraindicated as they may worsen seizures due to further inhibition of Nav1.1. 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 may benefit from a selective inhibitor of Nav1.6 include 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. We have demonstrated efficacy for seizures in an animal model with such an inhibitor. We anticipate filing an IND for a drug candidate to treat DS in 2016. Given the orphan nature of this disorder, we believe that DS may represent an attractive opportunity for us to advance independently.

XEN801 for the Treatment of Acne

XEN801 is a selective, small molecule inhibitor of stearoyl Co-A desaturase, or 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. 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.

XEN801 is currently in IND-enabling studies, and we anticipate filing an IND or IND equivalent application to initiate a Phase 1 trial in the second quarter of 2015 and initiating a proof-of-concept Phase 2 trial in the second half of 2015. We believe a selective, small-molecule inhibitor of SCD1 has therapeutic potential for skin disorders such as moderate to severe acne, seborrhoea and sebaceous hyperplasia.

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. 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.

New Pipeline Opportunities

Given the commercial opportunity and the pharmaceutical industry’s interest in the pain market, we are using our Extreme Genetics discovery platform and specialized insights into the biology of pain to identify new drug targets for this common medical problem. We formed a second collaboration with Genentech in March 2014 for pain genetics, pursuant to which we intend to focus on rare phenotypes where individuals have an inability to perceive pain or where individuals have non-precipitated spontaneous severe pain. 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 severe pain phenotypes, such as paroxysmal extreme pain disorder, or PEPD, inherited EM and cluster headache.

In addition to our study of rare human disorders of extreme pain or the absence of pain, we are studying other rare disorders with extreme phenotypes that we believe could yield new drug targets in disorders where high medical need exists, such as neurological disorders like essential tremor.

In addition, 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.

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 with the advantage of having a greater understanding of the role of the drug target in human disease.

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:

- 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;
- 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;
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internal capabilities in genome sequencing, molecular biology and bioinformatics to enable identification of single-gene defects and validation of these as potential drug targets; and

- 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.

Our Extreme Genetics discovery platform has proven to be a valuable asset for our company over the years. It has led to a robust pipeline, including an approved product, two development programs, and three preclinical programs. Our platform has also allowed us to attract numerous collaborations with leading pharmaceutical companies, including Teva, Genentech, and Merck, that have in aggregate generated more than $150.0 million in non-equity funding through December 31, 2014 and provide us with research funding and the potential for more than $1.0 billion of research, development, regulatory and sales-based milestone payments, as well as royalties on net product sales.

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 have been able to identify new binding sites on ion channels which, in turn, has 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.

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 UBC, we demonstrated that humans with a variant of the LPL gene called LPL^{S447X} 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^{S447X} variant. We believe that the introduction of the therapeutic LPL^{S447X} 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 or North America. 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. Glybera was developed by our licensee, uniQure. 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. We believe that Chiesi plans to launch Glybera in the first quarter of 2015 in Europe, and that uniQure is pursuing a U.S. product approval strategy with plans to file a BLA with the FDA following receipt of the results from a planned Phase 4 trial expected to begin in mid-2015. Glybera has received orphan drug designation for the treatment of LPLD in both the EU and the U.S. 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. 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 product.

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^{S447X}

Together with our collaborators at UBC and using our Extreme Genetics discovery platform, we demonstrated that the LPL^{S447X} 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^{S447X} 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. We believe that Chiesi plans to launch Glybera in the first quarter of 2015 in Europe, and that uniQure is pursuing a U.S. product approval strategy with plans to file a BLA with the FDA following receipt of the results from a planned Phase 4 trial expected to begin in mid-2015. Glybera has received orphan drug designation for the treatment of LPLD in both the EU and the U.S.

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 potentially broad application in nociceptive pain, mediated by damage or injury to tissues, including the pain sensitivity caused by inflammation, and neuropathic pain mediated by damage, dysfunction, or injury of nerves. TV-45070 is partnered with Teva. Pursuant to the terms of the agreement, Teva is obligated to complete three Phase 2 or later stage clinical trials. Using a topical ointment formulation of TV-45070, Teva has initiated a 300-patient, randomized Phase 2b clinical trial in OA of the knee, and data are expected in the third quarter of 2015. Teva is also developing topical TV-45070 in neuropathic pain indications, and is planning a Phase 2b clinical trial in patients with PHN with patient enrollment expected to begin in March 2015.

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. Under the terms of the agreement, Teva made an upfront payment to us of $41.0 million. 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 sales-based milestone payment of $30.0 million. 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 that such products are covered by the licensed patents and in certain other instances. We also have an option to co-promote products in the U.S. Prior to our entry into the 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 OA (November 2013).

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. CIP patients are unable to feel pain for painful events including fractures, childbirth, osteomyelitis and OA, 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. Topical TV-45070 in animal models has been shown to exhibit anti-inflammatory properties and may be suited to peripherally-based inflammatory pain such as joint arthritic pain. 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.

TV-45070 Clinical Development

Topical and oral formulations of TV-45070 have been studied in Phase 1 clinical trials in healthy volunteers and in four Phase 2 proof-of-concept clinical trials. A 300-patient, randomized Phase 2b clinical trial in OA is ongoing and future clinical development in post-herpetic neuralgia is planned.

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 not observed.

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

We believe that TV-45070, if successfully developed and approved, may have broad market potential as a pain drug. The types of pain that CIP patients cannot perceive suggest that Nav1.7 may be involved in pain signaling for different types of painful stimuli including both nociceptive, such as inflammatory-based pain, and neuropathic pain. The current standards of care for such prevalent forms of pain often provide poor efficacy and dose increases to provide improved efficacy are often limited by poor tolerability including common side effects, such as nausea,

dizziness and sleepiness. Certain anti-inflammatory pain medications, including those used to treat OA, have FDA black box warnings for gastrointestinal bleeding and cardiovascular events, both of which can be fatal. Despite currently available treatments for prevalent pain disorders, we believe that there may be subpopulations of pain patients with unmet medical needs, which topical TV-45070 may be able to address given its novel mechanism and local site of action. Given its novel mechanism, we also expect that topical TV-45070 could be used as either a single agent or in combination with other analgesics that work through different mechanisms.

Based on the potential broad utility of TV-45070, prior to our collaboration with Teva, we had 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 an oral Phase 2 clinical trial in third molar tooth extraction; a topical Phase 2 clinical trial in postherpetic neuralgia; and two (one oral and one topical) Phase 2 clinical trials in the orphan indication EM. In contrast to the absence of pain in CIP, where Nav1.7 is deficient, over activity of Nav1.7, including genetic gain of function mutations that increase the Nav1.7 mediated pain signaling, can cause the spontaneous pain of primary EM. Primary EM is a condition of EM that is not caused by another disease or disorder. Furthermore, EM represents a high treatment hurdle as the majority of EM patients do not experience adequate pain relief from current drugs approved for the treatment of pain.

Oral TV-45070 Trial in Nociceptive Inflammatory Pain

We conducted a trial for third molar tooth extraction, which is an established acute inflammatory pain model. The data from this proof-of-concept trial support future development of TV-45070 for nociceptive pain indications, including OA.

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.

DESIGN	KEY SAFETY DATA	KEY EFFICACY DATA
Double-blind, randomized, placebo-controlled	Safe and well tolerated	The primary and secondary endpoints showed consistent trends in favor of reduced pain for TV-45070 versus placebo
61 subjects randomized	The most frequently reported adverse events, or AEs, were nausea, dizziness, headache and drowsiness, which were mild or moderate in intensity	The primary endpoint of TOTPAR-6 showed a separation between active and placebo but did not reach the pre-defined statistical significance for the trial
Single oral dose of 500 mg or placebo	No SAEs	Certain secondary endpoints achieved statistical significance
		In a post-hoc analysis, a significantly increased proportion of TV-45070-treated patients reported 30% or greater and 50% or greater reduction in their pain compared to placebo

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, or TOTPAR-6. For this endpoint, 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. The figure below illustrates the greater pain relief of TV-45070 versus placebo and a greater separation between TV-45070 and placebo at subsequent observations, including 8, 10, and 12 hours, suggesting improved effect over time.

Multiple secondary endpoints were studied including Categorical Pain Relief Rating Scale, or REL, a numerical five-point scale ranging from no pain to complete pain and Pain Intensity Difference, or PID, compared to baseline. Certain secondary endpoints for the REL achieved predefined statistical significance for this trial.

An exploratory analysis not described within the study protocol submitted to the FDA demonstrated a statistically significant proportion of subjects on TV-45070 exhibited a 30% or greater ($p<0.05$) (see figure below) and 50% or greater ($p<0.05$) reduction in pain compared to placebo. These improvements were observed from approximately 1.5 to 19 hours post-dosing, suggestive of an extended clinical effect after a single oral dose.

The data from this proof-of-concept trial support future development of TV-45070 for nociceptive pain indications, including OA.

TV-45070 in Neuropathic EM Pain

TV-45070 has been 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. The table below summarizes the results of these TV-45070 trials:

Oral Phase 2 EM Trial

DESIGN	KEY SAFETY DATA	KEY EFFICACY DATA
Double-blind, randomized, placebo-controlled crossover Four primary EM patients randomized 400 mg or placebo was dosed twice daily for two days	Most common AEs were dizziness and drowsiness that ranged from mild (no interference in daily activities) to severe (significant interference in daily activities) No SAEs or deaths, with the most frequently reported AEs being dizziness, headache, sedation and drowsiness	A significant (42%) reduction in EM pain was observed in the three patients where pain was induced (p=0.014)

Topical Phase 2 EM Trial

DESIGN	KEY SAFETY DATA	KEY EFFICACY DATA
Double-blind, randomized, placebo-controlled Eight primary EM patients randomized 8% ointment or placebo was dosed twice daily for two or three weeks	Safe and well tolerated Low plasma exposures No meaningful central nervous system side effects No drug-related SAEs, or deaths, with local application site reactions being the most common drug-related AE reported	Three of seven patients (43%) on TV-45070 showed consistent clinically meaningful reductions in induced and daily pain compared to baseline Four of six (67%) patients on TV-45070 who used rescue cooling showed a reduction in cooling usage compared to baseline Six of seven (86%) patients on TV-45070 had an improvement in sleep interference scores compared to baseline

Oral TV-45070 Phase 2 Trial in EM

We conducted a small Phase 2 proof-of-concept trial with oral TV-45070 in patients with primary EM. This exploratory trial, which was published in the journal Pain, Goldberg, Y.P. et al Pain 153 (2012) 80-85, was a randomized, double-blind, placebo-controlled, two-period crossover design 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.

We developed a novel pain induction method for assessing the response of TV-45070 using an electric heater placed at a standardized distance from the subject's feet. Three patients with episodic EM pain were subjected to heat or exercise on up to six occasions during each treatment period to induce a controlled painful flare. One patient who was in constant, severe pain was not induced. Mean total pain intensity scores were measured for the two hours following each pain induction over the two day treatment period with either TV-45070 or placebo. The amount of pain following induction was calculated by quantifying the area under the pain intensity curve for two hours following induction, or AUC0-2hrs.

Improvements in pain efficacy measures in all four subjects were observed, with statistically significant reductions in pain scores in the three subjects in whom pain was induced. The amount of pain in the two hours following induction was reduced by 21% (p = 0.011), 33% (p = 0.004) and 88% (p = 0.031) in these three patients, respectively. Overall, in these three subjects, pain was reduced by 42% on TV-45070, compared to placebo (p = 0.014). The subject who was in constant pain and was not induced, showed a mild reduction in pain at various time points during the TV-45070 dosing period.

In the following figure, these data are presented as a mean AUC0-2hrs for the three subjects as a percentage of placebo who underwent pain induction either by step exercise or by heat. A 42% reduction in the amount of induced pain was observed on average with TV-45070 compared to placebo (p=0.014). These data support our belief in the ability of TV-45070 to inhibit human Nav1.7 mediated pain signaling which supports the predicted mechanism of action.

Topical TV-45070 Phase 2 Trial in EM

We conducted a small Phase 2 proof-of-concept trial with TV-45070 ointment in patients with primary EM. This exploratory trial was a randomized, double-blind, placebo-controlled design with eight subjects (seven TV-45070 and one placebo) comparing 8% TV-45070 to placebo applied two times per day to the feet for a duration of 14 or 21 days. We evaluated multiple endpoints for each subject to increase our understanding of the effect of TV-45070, including the amount of pain in response to a heat stimulus, the frequency and duration of cooling to provide relief from their painful flares, changes in daily pain scores and the degree of sleep interference. Throughout the trial, TV-45070 plasma concentrations were low and TV-45070 was well-tolerated. Consistent with these low plasma levels, there was no treatment-related dizziness and drowsiness and there were no treatment-related SAEs. Dizziness and drowsiness are common side effects for many currently prescribed centrally-acting analgesics. Local application site reactions were the most common drug-related AEs observed.

In this trial, three of the seven (43%) TV-45070-treated subjects responded positively based on the magnitude and consistency of improvement across the measured efficacy parameters. While the four remaining TV-45070-treated subjects were considered to be non-responders based on their magnitude of response or inconsistent response or both, some improvements were seen in certain efficacy parameters, in particular, sleep and rescue cooling. Similarly, the placebo-treated subject did not show a consistent pattern of response.

Four of the seven (57%) subjects receiving TV-45070 treatment responded to the standard heat inductions compared to pre-treatment. Three of these seven (43%) subjects showed more than 50% improvements in their ability to tolerate and/or recover from the heat inductions. In addition, these three subjects demonstrated clinically meaningful improvements (a one-point, or 30% or greater reduction) in the level of daily pain experienced during the outpatient treatment period compared to pre-treatment. The remaining TV-45070-treated subjects and the placebo-treated subject responded inconsistently or demonstrated deteriorations in their responses compared to baseline.

EM patients may seek relief by immersing their limbs in cold or ice water to help manage their painful flares. If a patient uses less cooling when on TV-45070, this may indicate the product is reducing the number and/or intensity of their EM flares. Four of the six (67%) TV-45070-treated subjects who used cooling at baseline showed a reduction in cooling usage while on treatment. In contrast, the placebo-treated subject cooled for substantially longer during the outpatient period compared to pre-treatment.

Unlike the placebo-treated subject, subjects on TV-45070 used less rescue cooling compared to their baseline measurements. The amount of daily cooling usage, including cooling frequency and cooling duration, for subjects on TV-45070 or placebo as a percentage change from baseline is shown below. This small exploratory trial was not designed to reach statistical significance of p £ 0.05, and no such statistical significance was found.

EM flares often wake patients several times each night and an improvement in the sleep interference scores could indicate that TV-45070 may reduce the number and/or intensity of the flares during sleep. Six of the seven (86%) subjects receiving TV-45070 treatment showed improvements in their daily sleep interference scores during treatment compared to baseline, with three subjects demonstrating at least 50% improvements. In five of the six (83%) subjects this was associated with less or no cooling usage. The placebo-treated subject also demonstrated a reduction in sleep interference; however, as with the daily pain scores, the interpretation of this response is confounded by the greater cooling usage by this subject.

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, including OA and PHN, and has no current development plans for TV-45070 in EM.

Topical TV-45070 Trial in Postherpetic Neuralgia, or PHN

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 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.

DESIGN	KEY SAFETY DATA	KEY EFFICACY DATA
Double-blind, randomized, placebo-controlled, cross-over 70 subjects randomized 8% ointment or placebo administered twice daily for three weeks	Safe and well tolerated The most frequent AEs (greater than 5% frequency) included local application site reactions, nasopharyngitis and urinary tract infections, or UTIs Fewer related treatment emergent AEs for TV-45070 (18%) versus placebo (30%) Low plasma exposure No meaningful central nervous system side effects Less application site pain for TV-45070 (16% placebo versus 3% TV-45070) and pruritus, or itch, (13% placebo versus 3% TV-45070) No drug-related SAEs	There was a reduction in the primary efficacy endpoint (change from baseline in mean daily pain score) for TV-45070 and placebo, but the difference between treatments was not statistically significant Significantly increased proportion of TV-45070-treated patients reported 30% or greater (p=0.049) and 50% or greater (p=0.0078) reduction in their pain compared to placebo 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

Topical 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 UTIs.

There was a reduction in the primary efficacy endpoint (change from baseline in mean daily pain score) for TV-45070 and placebo, but the difference between treatments was not statistically significant. Multiple secondary endpoints were studied, including the proportion of subjects achieving at least 30% and 50% improvements in pain, the use of rescue analgesic medications, and the change in Daily Sleep Interference Scale score. A greater proportion of subjects on TV-45070 experienced a clinically meaningful reduction in their pain during the trial, which is a 30% or greater reduction in pain. A statistically significant larger proportion of subjects on topical TV-45070 exhibited a 30% or

greater (p=0.049) and a 50% or greater (p=0.0078) reduction in pain compared to placebo. A greater proportion of subjects on topical TV-45070 exhibited a statistically significant 30% or greater (p=0.034) improvement in sleep compared to placebo. Importantly, a slight trend to reduced use of rescue pain medication in the responders on TV-45070 was observed, suggesting rescue use did not explain the improved efficacy response in these subjects. These data support the development of topical TV-45070 as a treatment for PHN.

TV-45070 demonstrated a statistically significant increase in the proportion of clinically meaningful responders (30% or greater and 50% or greater reduction in pain) compared to placebo.

There is a relatively common genetic variant of Nav1.7 called the R1150W gene variant. We estimate that this variant has a frequency of 6% to 30% in different ethnic populations. Publications have reported that subjects with this variant who suffer from various painful disorders, including OA, report a greater amount of pain compared to those subjects who do not have this variant. Peripheral nervous system cell-based assays suggest this variant increases the activity of the Nav1.7 channel and the number of resultant nerve signaling action potentials. This increased activity may explain why patients with this variant feel more pain.

We genotyped 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. In our PHN trial there were eight carriers of this R1150W variant who were among the evaluable subjects. Of these carriers, five out of eight (63%) had a 30% or greater reduction in their pain when on topical TV-45070. 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. Due to these observations, stratification of subjects for R1150W is planned for Teva’s upcoming Phase 2bclinical trial of TV-45070 in PHN.

A larger proportion of Nav1.7 R1150W-carriers had a clinically meaningful 30% or greater response to TV-45070 than non-carriers.

Future Development Plans for TV-45070

We are collaborating with Teva on the development of topical TV-45070. Our agreement with Teva requires them to complete three Phase 2 or later stage clinical trials. Using a topical (ointment) formulation of TV-45070, Teva has initiated a 300-patient, randomized Phase 2b clinical trial in OA of the knee, and data are expected in the third quarter of 2015. Teva is also developing topical TV-45070 in neuropathic pain indications, and is currently planning a Phase 2b clinical trial in patients with PHN with patient enrollment expected to begin in March 2015..

Development of Topical TV-45070 for the Treatment of OA

Based on clinical proof-of-concept data of TV-45070 in the completed clinical trial of third molar tooth extraction, an established pain model of nociceptive pain, Teva has selected to develop topical TV-45070 for the treatment of nociceptive pain in knee OA and a randomized Phase 2b study is ongoing. The rationale supporting the development of TV-45070 in OA includes:

- Clinical proof-of-concept was observed with TV-45070 in the third molar extraction model of nociceptive pain.
- In preclinical models, topical TV-45070 has exhibited an ability to penetrate the knee joint and reside locally at relatively high concentrations while maintaining low plasma concentrations.
- We have identified a CIP patient with Nav1.7 deficiency and painless late stage OA of the knee.
- Published data for the R1150W variant suggest a role of Nav1.7 in OA pain.
- Application of TV-45070 to the human torso in Phase 1 and Phase 2 clinical trials to date showed low systemic exposure of TV-45070, which may in turn 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 OA patients have shown poor compliance with products that trigger common CNS side effects.
- Injections of lidocaine, a weak blocker of sodium channels, into human knee joints provides short term relief from OA pain providing pharmacological validation that a sodium channel inhibitor can provide relief from OA pain.

Teva filed an IND application with the FDA in November 2013 and, in the first quarter of 2014, commenced a Phase 2b single knee OA clinical trial. The trial is being conducted at approximately 35 U.S. sites and is a randomized, double-blind, placebo controlled study. Teva plans to enroll 300 patients who will be randomized to receive either placebo, 4% or 8% topical TV-45070. Patients will apply the treatment twice a day to the affected knee for four weeks.

The primary efficacy endpoint is the change from baseline to the last five days of treatment in average evening pain intensity in the treated knee when walking on a flat surface, as measured using the Western Ontario and McMasters Universities Arthritis Index, or WOMAC, scale. Secondary endpoints include the full WOMAC pain subscale, responder rates for 30% and 50% improvement in average evening pain intensity, the percentage of patients who are responders per Outcome Measures in Rheumatoid Arthritis Clinical Trials-Osteoarthritis Research Society International, or OMERACT-OARSI, criteria at week four, other quality of life assessments and various safety and pharmacokinetic analyses.

Exploratory efficacy analyses will also include stratification of the patients based on their R1150W status to evaluate the response to TV-45070 in the presence of this Nav1.7 variant.

We anticipate top line data from this study to be available in the third quarter of 2015 and, if positive, Teva plans to initiate a Phase 3 clinical trial.

About Osteoarthritis Pain

OA is a degenerative disorder that affects joints, most often the knees, hands, hips, spine and feet. It is characterized by the gradual deterioration of the cartilage in the joint often with joint space narrowing. The major symptom of OA is progressive pain, which may lead to stiffness and loss of mobility, as well as swelling around the joints. It has been estimated that approximately 9% of the U.S. population have pain associated with OA, which translates into approximately 28 million patients.

Arthritic pain, including OA, is generally thought to have an inflammatory component and is often treated with anti-inflammatory pain medicines, which work by inhibiting the effects of inflammatory molecules, such as prostaglandins. Acetaminophen and non-selective non-steroidal anti-inflammatory drugs, or NSAIDs, are generally considered the first-line therapy for OA. Non-selective NSAIDs are often replaced by selective NSAIDs that inhibit cyclooxygenase-2, or COX-2, for those individuals at risk of upper gastrointestinal, or GI, adverse reactions including bleeding, ulcers and perforation. If allowed to progress, these GI adverse events can be fatal and NSAID drugs have a FDA black-box warning for these reactions. Although the COX-2 selective inhibitors have a reduced risk of GI adverse reactions, they also have an increased risk of cardiovascular events that can be fatal. This cardiovascular risk led to some COX-2 products being withdrawn from the market and the addition of a black-box warning for such cardiovascular events. Despite limitations, these anti-inflammatory drugs are widely used in OA patients and provide relief from mild to moderate pain. Patients with severe symptomatic OA who fail to respond to these drugs often have joint replacement surgery and may require narcotics or injections of anesthetic agents into the arthritic joint while waiting for such surgery. We believe that the adverse effects associated with narcotics, especially in the elderly, and the difficulty of injections into the joint, combined with the large number of patients with moderate to severe OA, provide a significant market opportunity for a product with a novel mechanism, such as topical TV-45070. We believe that TV-45070 may avoid many of the efficacy limitations and adverse effects observed with acetaminophen, non-selective NSAIDS, COX-2 inhibitors and narcotics.

Development of Topical TV-45070 for the Treatment of Neuropathic Pain Indications

Teva is also developing topical TV-45070 for neuropathic pain disorders, including PHN. Teva expects to initiate patient enrollment in a Phase 2b clinical trial in PHN in March 2015. The rationale supporting the development of TV-45070 in PHN, includes:

· We observed 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.
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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.
- 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.

Teva has an IND with the FDA for the development of TV-45070 as a treatment of neuropathic pain, and is currently planning a Phase 2b clinical trial in patients with PHN with patient enrollment expected to begin in March 2015. The anticipated completion date for the PHN Phase 2b trial is in mid-2016.

The Phase 2b clinical trial in PHN will be a randomized, double-blind, placebo controlled, multi-site study to evaluate the efficacy and safety of TV-45070 in patients with PHN. The study will include three treatment groups to 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.

About Postherpetic 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 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, Roche, to discover and develop selective oral inhibitors of Nav1.7 for the treatment of pain. 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.

The first small-molecule, preclinical product candidate that was selected for development under our collaboration is GDC-0276. In September 2014, Genentech initiated a Phase 1 clinical trial for GDC-0276. The Phase 1 clinical trial has recently been expanded and is expected to complete enrollment in the second half of 2015. GDC-0276 is a selective, oral Nav1.7 small-molecule inhibitor being developed for the treatment of pain.

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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.

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 CTA for GDC-0276. We are also 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, plus a low single-digit percentage for large-molecule inhibitors of Nav1.7.

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.

Product Candidates in Discovery

Selective Small-Molecule Sodium Channel Inhibitors for the Treatment of Dravet Syndrome

We are developing selective inhibitors of the voltage-gated sodium channel Nav1.6 as a treatment for 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 DS.

DS is a severe form of childhood epilepsy that typically causes mental retardation and, in approximately 10% of cases, premature death before the age of 12 years. The frequency of DS in the U.S. has been estimated to be one in 20,000 to 40,000 births, which, when applied to U.S. federal census data, correlates to approximately 7,500 to 15,000 patients with DS in the U.S.

With our collaborators from McGill University, we identified the genetic link between rare human epilepsy and mutations in the Nav1.1 gene. 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 DS. To further support inhibiting Nav1.6 as a potential therapeutic approach to treat DS, 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.

DS is one of the most resistant epilepsies to treatment. Some benefit has been reported for drugs that increase the activity of the inhibitory brain pathways such as benzodiazepines and Stiripentol, while non-selective sodium channel blockers such as lamotrigine are contraindicated as they may worsen seizures due to further inhibition of Nav1.1. 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 may benefit from a selective inhibitor of Nav1.6 include 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 anticipate filing an IND for a drug candidate to treat DS in 2016. Given the orphan nature of this disorder, we believe that DS may represent an attractive opportunity for us to advance independently.

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.

XEN801 is currently in IND-enabling studies, and we anticipate filing an IND or IND equivalent application to initiate a Phase 1 trial in the second quarter of 2015 and we anticipate initiating a proof-of-concept Phase 2 trial in the second half of 2015. We believe a selective, small-molecule inhibitor of SCD1 has therapeutic potential for skin disorders such as moderate to severe acne seborrhoea and sebaceous hyperplasia.

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 proprionibacterium 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 potently reduces sebum production may be a significant treatment option for moderate to severe acne.

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. 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.

New Pipeline Opportunities

Given the commercial opportunity and the pharmaceutical industry's interest in the pain market, we are using our Extreme Genetics discovery platform and specialized insights into the biology of pain to identify new drug targets for this common medical problem. 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. 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 severe pain phenotypes such as PEPD, inherited EM and cluster headache.

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, such as neurological disorders like essential tremor. 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^{S447X}. Together with collaborators from UBC, we demonstrated that the LPL^{S447X} 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^{S447X} 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 for sales made by uniQure and its affiliates are reduced to a low single-digit in countries where the licensed technology and products are not covered by a valid patent claim. Such royalties are payable until the expiration of the last licensed patent from UBC. 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. We believe that Chiesi plans to launch Glybera in the first quarter of 2015 in the EU and that uniQure is pursuing a U.S. product approval strategy with plans to file a BLA with the FDA following receipt of the results from a planned Phase 4 trial expected to begin in mid-2015. With respect to uniQure's sublicense to Chiesi for the commercialization of Glybera in the EU and more than a dozen other countries including Brazil, China, Mexico and Russia, 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 (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 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.

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^{S447X}.

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^{S447X}.

Through December 31, 2014, we have paid to UBC upfront fees and milestone payments totaling CAD$230,000 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. Teva 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 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 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 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 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 and we are eligible for an additional $2.0 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, 2014, 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, 2014, we owned, co-owned or licensed 51 issued or allowed U.S. patents and approximately 25 pending U.S. patent applications, including provisional and non-provisional filings. We also owned, co-owned or licensed an additional 567 pending and granted counterpart applications worldwide, including 129 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 pending 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, if issued, is expected to expire in 2020 (absent any extensions of term). In addition, U.S. Patent No. 6,814,962, related European Patent No. 763,116, and pending counterpart U.S. Patent Application No. 13/584,203 have composition claims directed to various recombinant viruses containing LPL coding sequences and methods of using such viruses to treat various pathologies, and various other related patents and applications claiming priority to PCT/FR1995/00669 are directed to the preparation of recombinant viruses and uses in gene therapy, all of which are expected to expire in 2015 (absent any extensions of term).

As of December 31, 2014, we owned seven issued U.S. patents and six 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 50 foreign issued patents (exclusive of European patent national validation) and filed 123 corresponding applications in various foreign jurisdictions relating to TV-45070.

As of December 31, 2014, we, together with Genentech, co-owned two allowed U.S. patent applications, two pending U.S. patent applications and 26 pending counterpart patent applications worldwide relating to GDC-0276 and methods of making and using this and certain related compounds. Any patents issuing from these applications are expected to expire in 2033 (absent any extensions of term).

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.

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. As of December 31, 2014, we had 53 employees primarily engaged in research and development. Of these employees, 23 hold a Ph.D. degree or M.D. (or equivalent) degree. From time to time we engage individuals on a contractual basis for limited time periods. Our research and development expenses for the years ended December 31, 2014, 2013 and 2012 were $11.8 million, $12.3 million and $10.5 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.

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 products and product candidates 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^{S447X} genetic variant or otherwise.

TV-45070 and GDC-0276 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 for the treatment of pain, including Bioline Rx Ltd., Biogen Idec through its recently announced intention to acquire Convergence Pharmaceuticals Limited, Dainippon Sumitomo Co., Ltd. and Pfizer, 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.

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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, will 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;
- submission to the FDA of an NDA for drug products or a 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 AEs 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 AEs 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.

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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. On April 10, 2013, President Obama released his proposed budget for fiscal year 2014 and proposed to cut this 12-year period of exclusivity down to seven years. He also proposed to prohibit additional periods of exclusivity for reference biologics due to minor changes in product formulations, a practice often referred to as “evergreening.” 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 clinical trial application, or 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. For example, on August 2, 2011, the President signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional 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, which became effective on February 17, 2010. 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 will disclose the reported information on a publicly available website beginning in 2014. 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 others', 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, 2014, we had 74 employees, including 66 full-time employees. Of our employees, 53 were primarily engaged in research and development, and 23 of whom hold a Ph.D. or M.D. (or equivalent) degree. None of our employees is represented by a labor union. We have not experienced any work stoppages, and we consider our relations with our employees to be good.

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 reporting period since inception in 1996, and we do not expect to have sustained profitability for the foreseeable future. We had net losses of $4.3 million for the year ended December 31, 2012, and had an accumulated deficit of $103.7 million as of December 31, 2014.

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. 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.

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. To date, we have not generated any royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales other than from sales of Glybera under our license to uniQure Biopharma B.V., or uniQure, for the foreseeable future, if ever. 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, fails 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 a 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.

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.

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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, 2014, we incurred approximately $11.8 million of costs associated with research and development, exclusive of costs incurred by our collaborators in developing our current product and product candidates.

Our current cash and cash equivalents and marketable securities, including the net proceeds from our November 2014 initial public offering and concurrent private placement 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, and conducting preclinical research and clinical trials;
- whether our existing collaborations continue to generate substantial milestone payments and, ultimately, royalties on future 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 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, and changes in foreign currency exchange rates could impact our results of operations.

As of February 28, 2015, approximately 73% 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 and GDC-0276 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 June 2013, we paid Isis Pharmaceuticals, Inc., or Isis, an option exercise fee of $2.0 million to obtain an exclusive license to develop, manufacture and commercialize antisense products under our collaboration and license agreement with Isis; however, in the fourth quarter of 2013, we discontinued development of product candidates under this program as the preclinical data did not support the continued advancement of any product candidates.

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 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. 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;
- commercialization of competing products;
- sufficient commercial supply of Glybera;
- cost-effectiveness 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;
- 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.

To date, the FDA has never approved any gene therapy product as a treatment for any indication in the U.S. and the FDA may never approve Glybera. Any failure of uniQure or its sublicensee to successfully commercialize Glybera 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.

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 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^{S447X} 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 targeting Nav1.7 inhibitors to develop products to treat various pain indications, including Bioline Rx Ltd., Biogen Idec Inc. through its recently announced intention to acquire Convergence Pharmaceuticals Limited, Dainippon Sumitomo Co., Ltd. and Pfizer, Inc. Moreover, we are aware of various other product candidates in development that target other mechanisms of action to treat various pain indications. We are not aware of any drugs or therapies currently approved specifically for treating primary erythromelalgia, or EM.

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 likely to be 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. More restrictive government regulations or negative public opinion could have a negative effect on our business or financial condition and may delay or impair the commercialization of Glybera. If Glybera is not successfully commercialized, our ability to generate near term revenue could be impaired.

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 Pharmaceutical Industries Ltd., or Teva, is responsible for the on-going clinical development of TV-45070, and Genentech Inc., or Genentech, is responsible for the ongoing clinical development of GDC-0276. 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 and GDC-0276, 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 two clinical development candidates TV-45070 and GDC-0276. 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.

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 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.

Dr. Gary Bridger, our Executive Vice President of Research and Development, works for us on a part-time, one-day-a-week basis, pursuant to a consulting agreement. 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 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.

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.

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. 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 incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in North America;
- 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, 2014 and 2013, 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 the 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.

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;
- 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;
- 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 and GDC-0276 product candidates for treatment of pain 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.

In the case 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, 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 is 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;
·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.

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 to 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.

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 Dravet Syndrome, or 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.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively, PPACA, was enacted, which 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;

- 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 March 31, 2014 and by the 90th day of each subsequent calendar year, and disclosure of such information to be made on a publicly available website by September 2014;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians, effective April 1, 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, will have 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 on January 1, 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, coverage, 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 & Co., Inc., or 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 or commercialization of a product resulting 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 EEA 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.

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 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.

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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;

- 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 behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal Open Payments program, created under Section 6002 of PPACA and its implementing regulations requires 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) to report annually to HHS information related to "payments or other transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to HHS ownership and investment interests held by physicians (as defined above) and their immediate family members, with data collection required beginning August 1, 2013, reporting to the Centers for Medicare & Medicaid Services, or CMS, required by March 31, 2014 (and by the 90th day of each subsequent calendar year), and disclosure of such information to be made on a publicly available website by September 2014; 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.

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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 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

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future. This could cause the market price of our common shares to drop significantly, even if our business is doing well.

Sales of a substantial number of our common shares in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common shares and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that such sales may have on the prevailing market price of our common shares. As of February 28, 2015, we had 14,219,112 common shares outstanding, of which approximately 8.8 million shares are currently restricted as a result of securities laws or market stand standoff agreements, or lock-up agreements that prevent the holders of such shares from offering, selling, contracting to sell, pledging, or otherwise disposing (indirectly or otherwise) of any common shares or any securities convertible into or exchangeable for common shares, or entering into any swap hedge or other arrangements, subject to specified exceptions, for a period of 180 days after November 4, 2014. Our underwriters may, in their sole discretion, at any time, release all or any portion of the shares from the restrictions in the agreement with the underwriters. Moreover, holders of approximately 6.9 million shares of our common shares have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other shareholders. We have also registered all common shares that we may issue under our equity compensation plans. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up provisions described above.

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

Our stock price has fluctuated in the past and is likely to be volatile in the future. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. 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 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;
- expiration of contractual lock-up agreements with our executive officers, directors and security holders;
- 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.

Our executive officers, directors and principal shareholders will be able to exert significant influence over matters submitted to shareholders for approval.

As of March 6, 2015, our executive officers and directors (and their respective affiliated shareholders) in the aggregate, beneficially own shares representing approximately 21% of our outstanding common shares. As a result, if these shareholders were to choose to act together, they would be able to exert significant influence over matters submitted to our shareholders for approval, as well as our management and affairs. The interests of this group of shareholders may not always coincide with our corporate interests or the interests of other shareholders, and they may act in a way in which you may not agree with or in a way that may not be in the best interests of other shareholders. This concentration of voting power could delay or prevent an acquisition of our company on terms that other shareholders may desire or otherwise discourage a potential acquirer from attempting to obtain control of us, which in turn could have a material adverse effect on our share price.

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 stock is 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 will need 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, we expect these rules and regulations to make it more difficult and more expensive for us to obtain 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. We could be an “emerging growth company” for up to five years from the completion of our initial public offering. An independent assessment of the effectiveness of our internal controls could detect problems that our management’s assessment might not. In addition, our management and independent registered public accounting firm did not perform an evaluation of our internal control over financial reporting as of December 31, 2014, December 31, 2013 or December 31, 2012, 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, 2014, options to purchase 1,484,218 of our common shares with a weighted-average exercise price of $4.20 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 plan(s), 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 share-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.

Our management team will have broad discretion to use the net proceeds from our initial public offering and the concurrent private placement and its investment of these proceeds may not yield a favorable return. They may invest the proceeds of our initial public offering and the concurrent private placement in ways with which investors disagree.

Our management team will have broad discretion in the application of the net proceeds from our November 2014 initial public offering and the concurrent private placement and could spend or invest the proceeds in ways with which our shareholders disagree. Accordingly, investors will need to rely on our management team's judgment with respect to the use of these proceeds. These uses may not yield a favorable return to our shareholders. We intend to use the proceeds from the offering to: (1) fund preclinical and early clinical development of our DS and XEN801 programs; (2) to fund genetic research and drug discovery activities using our Extreme Genetics discovery platform; and (3) for working capital and other general corporate purposes. We may also use a portion of the net proceeds in connection with any exercise of co-development or co-promotion rights under our strategic alliances; however, no such rights are currently exercisable. In addition, we may also use a portion of the net proceeds to acquire, license and invest in complementary products, technologies or businesses; however, we currently have no agreements or commitments to complete any such transaction. These uses may not yield a favorable return to our shareholders.

We cannot specify with certainty all of the particular uses for the net proceeds received from our November 2014 initial public offering and the concurrent private placement. In addition, the amount, allocation and timing of our actual expenditures will depend upon numerous factors, including milestone payments received from our collaborations and royalties received on sale of our approved product and any future approved product. Accordingly, we will have broad discretion in using these proceeds. Until the net proceeds are used, they may be placed in investments that do not produce significant income or that may lose value.

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 is 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 1B. Unresolved Staff Comments
None.

Item 2. Properties
Our headquarters are located in Burnaby, British Columbia, where we occupy approximately 33,600 square feet of office and laboratory space. The term of the lease expires in March 2022. We currently pay an aggregate of approximately $77,502 per month in base rent, property tax, common area maintenance fees and management fees, and the landlord holds a security deposit equal to approximately $77,549. 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 began trading on The NASDAQ Global Market on 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 period indicated.

	High	Low
Year Ended December 31, 2014		
Fourth Quarter (commencing November 5, 2014)	$21.95	$9.21

Holders

As of February 28, 2015, there were approximately 371 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 graph shows a comparison from November 5, 2014 (the date our common shares commenced trading on The NASDAQ Global Market) through December 31, 2014 of the cumulative total return for our common shares, the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The graph assumes an initial investment of $100 on November 5, 2014 in each of our common shares, the NASDAQ Composite Index and the NASDAQ Biotechnology Index, and assumes reinvestment of dividends, if any. The comparisons in the graph are not intended to forecast or be indicative of possible future performance of our common shares.

Recent Sales of Unregistered Securities

In 2014, we granted options under our Amended and Restated Stock Option Plan to purchase 129,889 common shares to certain of our employees at exercise prices ranging from CAD$10.78 to CAD$11.22 per share and 33,943 common shares to our directors at exercise prices ranging from of CAD$10.78 to CAD$11.22 per share. In addition, in 2014 we granted options under our 2014 Equity Incentive Plan to purchase 36,008 common shares to our directors at an exercise price of USD$9.00 per share. During 2014, we issued an aggregate of 2,416 common shares that were not registered under the Securities Act to our employees pursuant to the exercise of options for cash consideration with aggregate exercise proceeds of approximately CAD$14,683. In addition, during 2014, we issued 13,365 common shares pursuant to subscription rights issued under a research funding agreement with Genome B.C.

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. The securities issued pursuant to subscription rights were issued pursuant to the Canadian prospectus exemption under section 2.3 of NI 45-106 as such securities were issued to an accredited investor, as such term is defined in NI 45-106.

Any grant of our stock options and any issuance of our common shares upon the exercise of such stock options described above that was made to a resident of the U.S. was made pursuant to written compensatory plans or arrangements with our directors, officers, employees and service providers in reliance on the exemption provided by Rule 701 promulgated under Section 3(b) of the Securities Act. All recipients either received adequate information about us or had access, through employment or other relationships, to such information.

On November 10, 2014, we completed a private placement in which we issued and sold 495,000 common shares to Roche Finance Ltd., or Roche, concurrently with the closing of our initial public offering. The sale and issuance of the common shares to

Roche was effected pursuant to the terms of a common share put agreement, dated as of March 19, 2014, with Roche. The aggregate purchase price of the common shares was USD$4,455,000, representing a per share price of USD$9.00, the price that our common shares were sold to the public in our initial public offering. The purchase price of the common shares was paid for by Roche in immediately available funds. The sale and issuance of the common shares was exempt from registration under the Securities Act under Section 4(a)(2) thereof as a transaction by an issuer not involving a public offering. Roche acquired the common shares for investment only and not with a view to or for sale in connection with any distribution of the common shares and appropriate legends were affixed thereto.

Use of Proceeds

On November 4, 2014, our registration statement on Form S-1 (No. 333-198666) was declared effective for our initial public offering, and on November 10, 2014 we completed the initial public offering consisting of 4,600,000 common shares for $9.00 per share. As a result of the offering, we received total net proceeds of approximately $34.2 million, after deducting total expenses of $7.2 million, consisting of underwriting discounts and commissions of $2.9 million and offering-related expenses of approximately $4.3 million. No payments for such expenses were made directly or indirectly to (i) any of our officers or directors or their associates, (ii) any persons owning 10% or more of any class of our equity securities, or (iii) any of our affiliates. Jefferies LLC and Wells Fargo Securities, LLC acted as joint book-running managers of the offering and as representatives of the underwriters. Canaccord Genuity Inc. acted as a co-manager for the offering.

There has been no material change in the planned use of proceeds from our initial public offering from that described in the final Prospectus dated November 4, 2014 filed with the SEC pursuant to Rule 424(b)(4).

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, 2014, 2013 and 2012 and Balance Sheet data as of December 31, 2014 and 2013 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, 2011 and Balance Sheet data as of December 31, 2012 and 2011 have been derived from our audited consolidated 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,			
	2014	2013	2012	2011
Statement of Operations Data:				
Revenue:				
Collaboration revenue	$28,366	$27,352	$14,300	$6,915
Royalties	4	4	8	3
	28,370	27,356	14,308	6,918
Operating expenses:				
Research and development	11,768	12,303	10,455	12,302
General and administrative	5,496	5,341	7,006	6,730
Total operating expenses	17,264	17,644	17,461	19,032
Income (loss) from operations	11,106	9,712	(3,153)	(12,114)
Other income (expense):				
Interest income	568	338	144	153
Interest expense	—	(64)	(93)	(91)
Foreign exchange gain (loss)	1,344	2,035	(169)	60
Gain (loss) on write-off and disposal of assets	—	11	(1,030)	—
Net income (loss)	13,018	12,032	(4,301)	(11,992)
Net income (loss) attributable to participating securities	—	8,199	—	—
Net income (loss) attributable to common shareholders	$13,018	$3,833	$(4,301)	$(11,992)
Net income (loss) per share—basic (1)	$4.11	$2.87	$(3.24)	$(9.06)
Net income (loss) per share—diluted (1)	$3.28	$1.91	$(3.24)	$(9.06)
Weighted-average common shares outstanding used in computing basic net income (loss) per share (1)	3,166	1,338	1,327	1,324
Weighted-average common shares outstanding used in computing diluted net income (loss) per share (1)	3,964	2,009	1,327	1,324

(1) See Note 3(l) 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,			
	2014	2013	2012	2011
	(in thousands)			
Balance Sheet Data:				
Cash, cash equivalents and marketable securities	$84,041	$49,276	$60,162	$14,924
Working capital	70,656	31,666	41,507	20,536
Total assets	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)	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 related notes included elsewhere in this Annual Report. The following discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially 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 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. Our Extreme Genetics discovery platform has yielded the first approved gene therapy product in the European Union, or the EU, a broad development pipeline and multiple pharmaceutical partnerships. 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 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 $150.0 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.

To date, our Extreme Genetics discovery platform has yielded:

- 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. We believe that uniQure's commercialization partner, Chiesi Farmaceutici S.p.A., or Chiesi, plans to launch Glybera in the first quarter of 2015;
- TV-45070 (formerly XEN402), a product candidate with four Phase 2 proof-of-concept clinical trials completed. Our partner Teva is conducting a 300-patient, randomized Phase 2b clinical trial in osteoarthritis, or OA, of the knee, with data expected in the third quarter of 2015 and is planning a Phase 2b clinical trial in patients with postherpetic neuralgia, or PHN, with patient enrollment expected to begin in March 2015;
- GDC-0276, a product candidate being developed in collaboration with Genentech for the treatment of pain. In September 2014, Genentech initiated a Phase 1 clinical trial for GDC-0276. The Phase 1 clinical trial has recently been expanded and is expected to complete enrollment in the second half of 2015. GDC-0276 is a selective, oral Nav1.7 small-molecule inhibitor being developed for the treatment of pain; and
- Proprietary preclinical programs, including a sodium channel inhibitor for the orphan disorder Dravet Syndrome, or DS, and XEN801, a stearoyl Co-A desaturase, or SCD1, inhibitor for the treatment of acne. We anticipate filing an investigational new drug, or IND, or IND equivalent application for XEN801 in the second quarter of 2015 and an

IND for our DS program in 2016.

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 2014, 2013 and 2012, we recognized revenue for an aggregate of approximately $28.4 million, $27.4 million and $14.3 million, respectively, consisting primarily of funding from our collaborators. Though our revenue from our collaboration and license agreements has 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 a net loss of $4.3 million for the year ended December 31, 2012 and had an accumulated deficit of $103.7 million as of December 31, 2014, from expenses incurred in connection with our research programs and from general and administrative costs associated with our operations.

We have not generated any royalty revenue or other revenue from product sales, and 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 2015, we announced that our partner Teva will initiate a Phase 2b clinical trial of TV-45070 in patients with post-herpetic neuralgia, or PHN. PHN is a painful complication of Herpes zoster infection. Herpes zoster, also 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.

The Phase 2b clinical trial in PHN will be a randomized, double-blind, placebo controlled, multi-site study to evaluate the efficacy and safety of TV-45070 in patients with PHN. The study will include three treatment groups to 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 is anticipated to be dosed in March 2015, and the anticipated completion date for the Phase 2b clinical trial is mid-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. To date, we have not generated any royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales other than from sales of Glybera under our license to uniQure 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 13” 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, 2014, 2013 and 2012 (in thousands):

	Year Ended December 31,		
	2014	2013	2012
uniQure:			
Milestone payment	$14	$531	$198
Teva:			
Recognition of upfront payment	12,255	13,143	927
Research funding	333	630	—
Genentech:			
Recognition of upfront payment	3,603	3,300	3,431
Research funding	4,248	4,514	3,517
Milestone payment	7,913	5,062	—
Merck:			
Recognition of initial milestone payment	—	—	1,060
Option fee	—	—	2,060
Research funding	—	—	2,442
Genome BC:			
Research funding	—	172	665
Total collaboration revenue	$28,366	$27,352	$14,300

Through December 31, 2014, 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 is being recognized as revenue ratably over the expected period of research performance of pre-commercial activities, which is 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 is being 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 received a $5.0 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 received an $8.0 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.

Pursuant to the terms of our agreement with Merck, we received an initial milestone payment of $5.0 million in February 2010. We determined that this initial milestone payment was not substantive and should not be considered a separate element. As such, we recognized the initial milestone payment of $5.0 million as revenue ratably over the expected period of research performance of pre-commercial activities, which was the period from February 2010 through June 2012. Since the beginning of 2011, we have received both an option fee and two milestone payments from Merck. Each of these payments was determined to be substantive and at risk at the inception of the agreement and as such have been recognized as revenue in the period received.

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 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, 2014, 2013 and 2012 (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Teva	$10,897	$24,691	$39,907
Genentech	882	3,115	6,745
Total deferred revenue	$11,779	$27,806	$46,652

We expect such deferred revenue remaining as of December 31, 2014 to be recognized as revenue in the applicable fiscal years ending December 31, 2015 and 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, 2014, 2013 and 2012 (in thousands):

	Year Ended December 31,		
	2014	2013	2012
Research and development	$11,768	$12,303	$10,455
General and administrative	5,496	5,341	7,006
Total operating expenses	$17,264		