Xenon Pharmaceuticals Inc.
Form 10-K
March 06, 2019

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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2018

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 No.)
200-3650 Gilmore Way Burnaby, British Columbia (Address of principal executive offices)	V5G 4W8 (Zip Code)

Registrant’s telephone number, including area code: (604) 484-3300

Securities registered pursuant to Section 12(b) of the Act: Common Shares, No Par Value; Common shares traded on The Nasdaq stock market

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

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES NO

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES NO

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

Indicate by check mark whether the Registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). YES NO

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
Emerging growth company	

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES NO

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the closing price of the common shares on The NASDAQ Stock Market on June 29, 2018, was approximately $147.5 million. Common shares held by each executive officer and director and by each other person who may be deemed to be an affiliate of the Registrant, have been excluded from this computation. This

determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of common shares of the Registrant outstanding as of March 1, 2019 was 25,751,266.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement relating to the 2019 Annual Meeting of Shareholders, which will be filed with the Securities and Exchange Commission subsequent to the date hereof, are incorporated by reference into Part III of this Report. 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, 2018.

XENON PHARMACEUTICALS INC.

FORM 10-K

For the Fiscal Year Ended December 31, 2018

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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 either from our internal research efforts or though acquiring or in-licensing other product candidates or technologies;
- the initiation, timing, cost, progress and success of our research and development programs, pre-clinical studies, and clinical trials;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- our ability to recruit sufficient numbers of patients for our current and future clinical trials for orphan or more common indications;
- our ability to achieve profitability;
- our ability to obtain funding for our operations, including research funding;
- our ability to receive milestones, royalties and sublicensing fees under our collaborations, and the timing of such payments;
- the timing and magnitude of potential milestone payments under our product acquisition and in-licensing agreements;
- the implementation of our business model and strategic plans;
- our ability to develop and commercialize product candidates for orphan and niche indications independently;
- our ability to advance XEN007, XEN496 and potentially other future product candidates directly into Phase 2 or later stage clinical trials;
- our commercialization, marketing and manufacturing capabilities and strategy;
- 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 any future products;
- the timing of, and our and our collaborators' ability to obtain and maintain, regulatory approvals for our product candidates;
- our ability to maintain and establish collaborations;
- our expectations regarding market risk, including interest rate changes and foreign currency fluctuations;
- our belief in the sufficiency of our cash, cash equivalents and marketable securities to meet our needs for at least the next 12 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. and its subsidiary. Unless otherwise noted, all dollar amounts in this report are expressed in United States dollars.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this Annual Report on Form 10-K, and although we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted a thorough inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

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

Item 1.Business

Overview

We are a clinical stage biopharmaceutical company committed to developing innovative therapeutics to improve the lives of patients with neurological disorders, including rare central nervous system, or CNS, conditions. We are advancing a novel product pipeline of neurology-focused therapies to address areas of high unmet medical need, with a focus on epilepsy.

To date, our pharmaceutical collaborations have generated in aggregate over $160.0 million in non-equity funding with the potential to provide us with future milestone payments, as well as royalties on product sales.

Our pipeline is summarized in the following figure, which shows our own proprietary product candidates and our partnered pain program with Genentech, a member of the Roche Group:

Our Strategy

Our goal is to build a self-sustaining, fully-integrated, and profitable company that discovers, develops and commercializes innovative CNS therapeutics.

Our strategy includes:

- Focusing on orphan and niche disease market opportunities that we can independently develop and commercialize.
- 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 additional product candidates.
- Identifying external opportunities to expand our pipeline.

A significant focus of our discovery efforts has been on 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.

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 more effective or safer therapeutics. We believe we have developed a core competence in identifying and developing selective small-molecule ion channel modulators, 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. In addition, we have complemented our internal discovery capabilities by identifying external product candidates that target ion channels in the CNS for the treatment of neurological conditions.

Our Product Candidates

XEN496, A Kv7 Potassium Channel Modulator for the Treatment of KCNQ2 Epilepsy

We are developing XEN496 (active ingredient ezogabine), a Kv7 potassium channel modulator, for the treatment of KCNQ2 epilepsy. Ezogabine was previously approved by the U.S. Food and Drug Administration, or FDA, as an anti-epileptic drug, or AED, as an adjunctive treatment for adults with focal seizures with or without secondary generalization. We believe published case reports where physicians have used ezogabine in infants and young children with KCNQ2 epileptic encephalopathy, or KCNQ2-EE (also known as EIEE7), indicate that XEN496 may be efficacious in this often hard-to-treat pediatric patient population.

We received orphan drug designation, or ODD, from the FDA for XEN496 as a treatment of KCNQ2-EE. A steering committee made up of key opinion leaders in the KCNQ2-EE and pediatric epilepsy fields has been established to help guide the clinical development of XEN496. In response to our pre-IND briefing package submission, the FDA indicated that it was acceptable to study XEN496 in infants and children up to 4 years old, and that a single pivotal trial in approximately 20 patients may be considered adequate in order to demonstrate XEN496's efficacy in KCNQ2-EE. We are currently finalizing a pediatric-specific formulation to complete pre-clinical formulation testing with a final drug product expected in the second quarter of 2019. We expect to file an Investigational New Drug, or IND, application in the third quarter of 2019, and, based on regulatory feedback, expect to initiate a Phase 3 clinical trial thereafter. This timeline is based on our assumption that the testing of our new XEN496 pediatric formulation in healthy adult volunteers will not be a regulatory requirement prior to initiating a Phase 3 clinical trial.

About KCNQ2-EE

KCNQ2 epileptic encephalopathy (KCNQ2-EE), otherwise known as EIEE7, is a rare, severe neurodevelopmental disorder with a significant seizure burden and profound developmental impairment. KCNQ2-EE is uniquely characterized by multiple, daily, refractory seizures presenting within the first week of life with a prominent tonic component and autonomic signs. Seizures are often accompanied by clonic jerking or complex motor behavior. The electroencephalogram, or EEG, at onset of the disease shows a burst suppression pattern later evolving into multifocal epileptiform activity. The infants usually develop a severe to profound intellectual disability with axial hypotonia which can be accompanied by limb spasticity. The seizure activity typically decreases with age with patients often becoming seizure free or experiencing more minor seizure burden by 3 to 5 years of age; however, thereafter seizures can reoccur in clusters. The intellectual disability and other co-morbidities are not reversed or improved with age and patients generally require life-long care. Patients are often non-verbal and some children may also have autistic features. Seizure-related bradycardia and oxygen desaturation with cyanosis have been observed, and are thought to contribute to the significant risk of Sudden Unexpected Death in Epilepsy, or SUDEP, in these children. KCNQ2-EE is rare, representing around 10% of patients with epileptic encephalopathy with onset in the first three months of life; however, the incidence of KCNQ2-EE is approximately 2.8/100,000 live births, which is roughly half the number of births of Dravet Syndrome, the most common genetic type of early infantile epileptic encephalopathy.

XEN1101, A Kv7 Potassium Channel Modulator for the Treatment of Epilepsy

We are developing XEN1101, a differentiated Kv7 potassium channel modulator, for the treatment of epilepsy and potentially other neurological disorders. We acquired XEN1101 from 1st Order Pharmaceuticals pursuant to an asset purchase agreement in April 2017. For a more detailed description of the terms of this agreement with 1st Order Pharmaceuticals, see "—Collaborations, Commercial and License Agreements" below.

The Kv7 potassium channel mechanism has been clinically validated with ezogabine, an earlier generation Kv7 modulator that was approved by the FDA as an adjunctive treatment for adults with focal seizures with or without secondary generalization. XEN1101's unique composition is chemically designed to improve upon potency, selectivity and pharmacokinetics, or PK, of ezogabine, and is not expected to have ezogabine's composition-specific tissue pigmentation effects.

Clinical Development

We announced final data from a XEN1101 Phase 1 clinical trial and the related transcranial magnetic stimulation, or TMS, studies at the American Epilepsy Society, or AES, Annual Meeting in December 2018. The objectives of the XEN1101 Phase 1 clinical trial were to evaluate the safety, tolerability and PK of both single ascending doses, or SAD, and multiple ascending doses, or MAD, using a powder-in-capsule formulation of XEN1101 in healthy subjects. The XEN1101 Phase 1 clinical trial also included a pharmacodynamics, or PD, read-out from TMS studies that were designed to assess XEN1101's ability and potency to modulate cortical excitability, thereby demonstrating activity in the target CNS tissue. The XEN1101 Phase 1 results include data from six SAD cohorts ranging in dose from 5 to 30 mg (n=34, placebo=8), including a crossover food effect cohort (n=10) with a single 20 mg dose. MAD results included three cohorts ranging in once daily doses from 15 to 25 mg (n=18, placebo=6) including two cohorts of 15 mg evaluated in a fasted and fed state over 7 and 10 days, respectively, and one cohort of 25 mg evaluated in a fed state over 10 days. The PK profile of XEN1101 (including an effective half-life greater than 24 hours) supports a once-per-day dosing schedule with expected steady state in approximately one week without the need for titration. The majority of adverse events, or AEs, were mild or moderate, resolved spontaneously and were consistent with antiepileptic drugs of this class. Sedation (including somnolence and drowsiness) and dizziness (including light-headedness and presyncope) were the most common AEs, while mild cognitive effects (including memory and speech impairment) and blurred vision were also observed in a dose dependent manner. There were no SAEs, deaths, or clinically significant delayed ventricular repolarization or laboratory findings. Phase 1 results suggest that that XEN1101 is generally safe and well tolerated in the doses examined (single doses of up to 30 mg and multiple doses of up to 25 mg once daily).

The Phase 1b double-blind, placebo-controlled, randomized cross-over TMS study included 20 healthy male subjects. TMS measurements were taken at 2 and 4 hours for all subjects and, due to a prolonged absorption phase displayed by XEN1101, an additional TMS assessment time-point was added at 6 hours for a subset of subjects. Subjects were randomized initially to either a 20 mg dose of XEN1101 or placebo and then, after a one week wash-out period, crossed over to the other treatment arm. XEN1101 reduced corticospinal excitability, as demonstrated by a concentration dependent elevation in resting motor threshold, or RMT, the key TMS-EMG measure. RMT increased in proportion to XEN1101 plasma concentration showing a mean ± standard error of mean increase of 4.9 ± 0.7% ($p<0.01$) at 6 hours. Active motor threshold, or AMT, also increased in proportion to plasma concentration of XEN1101 with an increase of 2.0 ± 0.4% at 6 hours. In addition, XEN1101 statistically significantly modulated TMS-evoked EEG potentials, or TEPs, in a pattern consistent with reductions in cortical excitability. Relative to time-matched placebo, at peak plasma levels, XEN1101 decreased the amplitude of TEPs vs placebo at 25, 45 and 180 ms after the TMS pulse. Additional measures of cortical excitability including global mean field power were similarly impacted. XEN1101 also shifted the power spectra of resting state EEGs toward lower frequencies. This Phase 1b TMS study provides evidence of the CNS effects of a 20 mg dose of XEN1101 as indicated by suppression of cortical

and corticospinal excitability, and helped with dose selection for our XEN1101 Phase 2b clinical trial.

Based on the encouraging Phase 1 and Phase 1b TMS data, we have initiated a Phase 2b clinical trial in adult patients with focal epilepsy. The Phase 2b clinical trial is designed as a randomized, double-blind, placebo-controlled, multicenter study to evaluate the clinical efficacy, safety and tolerability of XEN1101 administered as adjunctive treatment in adult patients with focal epilepsy. Approximately 300 patients will be randomized in a blinded manner to one of three active treatment groups or placebo in a 2:1:1:2 fashion (XEN1101 25 mg : 20 mg : 10 mg : Placebo). The primary endpoint is the median percent change in monthly focal seizure frequency from baseline compared to treatment period of active versus placebo. An IND application for XEN1101 has been accepted by the FDA, and site selection and patient enrollment are now underway for the XEN1101 Phase 2b clinical trial in the United States, Canada and Europe. Depending upon the rate of enrollment, top-line results from the XEN1101 Phase 2b clinical trial are anticipated in the second half of 2020.

About Focal Seizures

A focal seizure is localized within the brain and can either stay localized or spread to the entire brain, which is typically categorized as a secondary generalized seizure. Focal seizures are the most common type of seizure experienced by people with epilepsy. The treatment of an individual patient with focal seizures is currently focused on reduction of seizure frequency, with seizure freedom as the ultimate goal. Focal seizures (simple, complex and secondarily generalized tonic-clonic) account for approximately 60% of seizures (GlobalData Report 2017) of which approximately 33% are considered resistant to current treatments (Epilepsy Foundation). It is estimated that the addressable population in the United States could include approximately 460,000 adults and 70,000 pediatric epilepsy patients with refractory seizures.

XEN901, A Selective Nav1.6 Sodium Channel Inhibitor for the Treatment of Epilepsy

We are developing XEN901, a potent, highly selective Nav1.6 sodium channel inhibitor, for the treatment of epilepsy. By selectively targeting Nav1.6, it is anticipated that XEN901 may achieve efficacy conferred by this well-validated epilepsy target, but with a potentially improved therapeutic index compared with currently available non-selective sodium channel inhibitors.

There is strong human genetic validation supporting the rationale for treating epilepsy by blocking the Nav1.6 sodium channel. Nav1.6 is the most highly expressed sodium channel in the excitatory pathways in the CNS. When mutations in the SCN8A gene, which encodes the Nav1.6 sodium channel, result in a gain of function in the Nav1.6 sodium channel, children can present with a very severe form of SCN8A Epileptic Encephalopathy, or SCN8A-EE, also known as EIEE13.

Clinical Development

In February 2018, we initiated a randomized, double-blind, placebo-controlled Phase 1 clinical trial to evaluate XEN901's safety, tolerability and PK in both SAD and MAD cohorts of healthy adult subjects. We announced results from the XEN901 Phase 1 clinical trial and the related pilot TMS study at the AES Annual Meeting in December 2018.

The XEN901 final Phase 1 results include data from six SAD cohorts ranging in dose from 5 to 80 mg (n=30, placebo=10) and from four MAD cohorts ranging in dose from 15 mg twice daily to 75 mg once daily (n=23, placebo=7). A food effect cohort (n=9) was also conducted with single doses of XEN901 in fed and fasted states in a crossover design. In addition, XEN901's effects on TMS measurements and EEG were assessed in two of the multiple dose cohorts. A tablet formulation of XEN901 was also assessed in a single dose cohort of 45mg (n=6; placebo=2) and a multiple dose cohort of 45mg twice daily (n=6; placebo=2). Favorable PK data show dose proportionality with predicted half-life of 8 to 11 hours suggesting that XEN901 could be compatible with a once or twice daily dosing regimen. The majority of AEs for the SAD, MAD, and food effect cohorts were deemed unrelated to XEN901, were mild or moderate, transient and resolved spontaneously. All AEs considered possibly related to XEN901 were mild; only muscle twitching, nausea and dizziness were reported in more than 1 subject. There have been no SAEs, deaths, or clinically significant ECG, vital signs or laboratory findings. The interim preliminary safety results suggest XEN901 is overall generally safe and well tolerated in the doses examined.

XEN901's effects on TMS measurements and EEG were assessed in a subset of 8 subjects from the 50 and 75 mg once daily cohorts and compared to 3 placebo subjects. TMS measures were recorded at baseline and on Day 5/6. In this pilot study, XEN901 showed increases in RMT of 2.0% (versus 0.67% in placebo); increases in AMT of 2.25% (versus 0% in placebo); decrease in amplitude of TEP at 180 ms (P180), and an increase in delta power in the resting state EEG. The observed changes in TMS-EMG and TMS-EEG parameters suggest activity of XEN901 in the target

CNS tissue in this exploratory pilot study.

The next steps for XEN901 include continued planning for Phase 2 or later clinical development to evaluate XEN901 as a treatment for adult focal seizures or for rare, pediatric forms of epilepsy, including SCN8A-EE patients, depending on feedback from planned discussions with regulatory agencies. We expect to receive regulatory feedback on the requirements to advance XEN901 into pediatric SCN8A-EE patients in the second quarter of 2019, and pediatric formulation development and juvenile toxicology studies are underway to support future pediatric development activities.

About SCN8A Epileptic Encephalopathy

SCN8A Epileptic Encephalopathy (SCN8A-EE), also known as EIEE13, is a rare, extremely severe, single-gene epilepsy caused by mutations in the SCN8A gene that result in a gain-of-function in the Nav1.6 sodium channel. SCN8A-EE typically presents with seizure onset between birth and 18 months of age. Most children diagnosed with SCN8A-EE have seizures that can occur multiple times a day and are often difficult to treat. Other symptoms include learning difficulties, muscle spasms, low or high muscle tone, poor coordination, developmental delay, and features similar to autism. The extent of physical disability leaves some children able to make little or no voluntary movement. Most children will have trouble learning to speak, and some will need assistance from feeding tubes to get the nourishment they need to grow. It is also believed that children and teenagers with SCN8A-EE are at risk for SUDEP.

XEN007, A CNS-acting Calcium Channel Modulator

XEN007 (active ingredient flunarizine) is a CNS-acting calcium channel modulator that modulates Cav2.1 and T-type calcium channels. Other reported mechanisms include dopamine, histamine and serotonin inhibition. Flunarizine is available in certain countries outside of the United States, and has been reported to have clinical benefit in treating migraine and other neurological disorders, including hemiplegic migraine, or HM, alternating hemiplegia of childhood, or AHC, vertigo, and as adjunctive treatment in certain epilepsies.

The FDA has granted a rare pediatric disease, or RPD, designation for the treatment of AHC with XEN007. We previously received ODD from the FDA for XEN007 for the treatment of both AHC and HM. In addition, we have entered into key exclusive licensing agreements in order to access regulatory files and drug product manufacturing, both of which may enable advanced clinical development of XEN007. Various development strategies for XEN007 are under consideration, including the support of at least one Phase 2 (or later stage) clinical trial in an orphan neurological indication, with initiation anticipated in 2019.

New Pipeline Opportunities

Given our expertise in ion channel drug discovery, our efforts are concentrated on the identification of ion channel targets where we believe novel modulators might represent significant therapeutic advances, with a particular focus on CNS-related orphan indications. We intend to expand our pipeline from our internal research efforts and through the acquisition or in-licensing of other product candidates.

Our Partnered Programs

Selective Inhibitors of Nav1.7 for the Treatment of Pain

In December 2011, we entered into a collaborative research and license agreement with Genentech and its affiliate, F. Hoffman-La Roche Ltd, or Roche, to discover and develop selective oral inhibitors of Nav1.7 for the treatment of pain. For a more detailed description of the terms of this agreement with Genentech, see “—Collaborations, Commercial and License Agreements” below. Based on our discovery of Nav1.7 deficiency underlying the rare human disease called congenital indifference to pain, or CIP, where individuals with CIP are unable to feel pain, we believe that Nav1.7 is a highly-validated target for the treatment of pain. Our Genentech collaboration is focused on discovering and developing oral drugs that selectively target 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. 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.

Genentech had been focused on the development of GDC-0310, but after completing an analysis of additional pre-clinical studies with GDC-0310 and reviewing the totality of data available, Genentech decided to discontinue further clinical development of GDC-0310 and elected to focus its future Nav1.7 development efforts on back-up molecules.

Additional Collaborative Work with Genentech

We formed a second collaboration with Genentech in March 2014 for pain genetics, with a 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. In March 2017, the research term for this second collaboration agreement was extended until March 2018. Under that agreement, Genentech has paid us a $1.5 million upfront payment and two $0.25 million milestone payments related to the identification of novel pain targets in September 2015 and July 2017. For a more detailed description of the terms of our collaborations with Genentech, see "—Collaborations, Commercial and License Agreements" below.

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. For a more detailed description of the terms of our agreement with Merck, see "—Collaborations, Commercial and License Agreements" below. In 2012, Merck exercised its option to obtain an exclusive license to a target for cardiovascular disease and compound inhibitors that were discovered during the research collaboration. The target, when inhibited, is predicted to provide a beneficial lipid profile with the goal of protecting from cardiovascular disease.

Collaborations, Commercial and License Agreements

Asset Purchase Agreement with 1st Order Pharmaceuticals, Inc.

In April 2017, we entered into an asset purchase agreement with 1st Order Pharmaceuticals, Inc., or 1st Order, pursuant to which we acquired all rights with respect to XEN1101 (previously known as 1OP2198). 1st Order previously acquired 1OP2198 from Valeant Pharmaceuticals Luxembourg S.a.r.l., an indirect subsidiary of Bausch Health Companies Inc., together with Valeant Pharmaceuticals Ireland Limited, Bausch Health, and assumed certain obligations, including potential milestone and royalty payments. Under the terms of the asset purchase agreement, we paid 1st Order an upfront fee of approximately $0.4 million and a $0.7 million milestone in 2017 upon achieving a clinical development milestone.

In September 2018, we signed an agreement with Bausch Health to buy out all future milestone payments and royalties owed to Bausch Health with respect to XEN1101, including up to $39.6 million in potential clinical development, regulatory and sales-based milestones and a mid-to-high single digit percentage royalty on commercial sales in exchange for a one-time payment of $6.0 million. We remain responsible for future potential payments to 1st Order of $0.5 million in clinical development milestones, up to $6.0 million in regulatory milestones for multiple indications and $1.5 million in other milestones, which may be payable pre-commercially. There are no royalty obligations to 1st Order.

Agreements with Genentech for 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 a compound for development and an $8.0 million milestone payment upon the approval by Health Canada of a CTA. Genentech provided funding to us for certain of our full-time equivalents, or FTEs, performing the research collaboration plan, which concluded in December 2016. 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 pre-clinical 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 pre-commercial and commercial milestone payments and royalties may be subject to reductions based on the period in which the compound that is selected for development and commercialization was initially conceived.

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.

Our collaborative research and license agreement with Genentech has been amended multiple times, in May 2015, November 2015, March 2016, May 2017, July 2018 and September 2018, to either extend the term of the research program or to provide us with greater flexibility in developing compounds that target Nav1.6. Pursuant to the current amendment, we have obtained a non-exclusive, irrevocable, perpetual, world-wide, sublicensable license under the know-how forming part of the Genentech intellectual property developed under the Nav1.7 collaboration that is necessary or useful to make, use, sell, offer for sale, and import compounds from our Nav1.6 program that are above a certain potency threshold on Nav1.7 and products containing those compounds. Our license from Genentech includes commercialization rights but we are restricted from developing or commercializing our Nav1.6 compounds below a certain potency on Nav1.7 in the field of epilepsy and any of our Nav1.6 compounds, regardless of their potency on Nav1.7, in the field of pain. In exchange for the rights granted to us under this amendment, Genentech is eligible to receive a low single-digit percentage, tiered royalty on net sales of our Nav1.6 compounds, including XEN901, for a period of ten years from first commercial sale on a country-by-country basis. Pursuant to the amendment, we granted Genentech a royalty-free, non-exclusive, world-wide license under our Nav1.6 intellectual property to make, use, sell, offer for sale and import compounds below a certain potency on Nav1.7 and products containing those compounds for all uses and indications except epilepsy.

In March 2014, we entered into an additional agreement with Genentech for pain genetics, which focused 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 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 two $0.25 million milestone payments related to the identification of novel pain targets in September 2015 and July 2017. Genentech’s time-limited, exclusive right of first negotiation, which was exercisable throughout the research term, expired at the same time as the agreement in March 2018. Despite such termination, we remain eligible for up to an additional $1.5 million in milestone payments.

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 discovery platform. Through December 31, 2018, 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 pre-clinical 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 low 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.

Termination Agreement with Teva

On March 7, 2018, we and Teva Pharmaceuticals International GmbH and Teva Canada Limited, or together Teva, entered into a termination agreement terminating by mutual agreement the collaborative development and license agreement dated December 7, 2012, as amended, which subsequently closed on March 27, 2018. In connection with the termination, Teva returned and we cancelled 1,000,000 of our common shares that were owned by Teva. Pursuant to the terms of the termination agreement, Teva has also returned, licensed or assigned to us certain intellectual property, including certain patent rights and transferred regulatory filings related to TV-45070. The termination agreement requires us to pay a low single digit percentage royalty to Teva based on net sales of approved products, if any, resulting from any continued development and commercialization of TV-45070 by us or a sublicensee during the period that assigned or licensed patents cover such products. To date, no such sales have occurred.

Intellectual Property

As part of our business strategy, we generally file patent applications disclosing and claiming drug targets and their novel uses, 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 European Union, or 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, 2018, we owned, co-owned or licensed 30 issued U.S. patents and approximately 18 pending U.S. patent applications, including provisional and non-provisional filings. We also owned, co-owned or licensed an additional 106 pending and granted counterpart applications worldwide, including 24 country-specific validations of four European patents.

As of December 31, 2018, we owned two issued U.S. patents and one U.S. provisional patent application related to XEN1101, and methods of making and using XEN1101 and certain related compounds. The issued patents are expected to expire between 2028 and 2029 (absent any extensions of term). In addition, we have 13 foreign issued patents (exclusive of European patent national validations) and have six pending corresponding applications in various foreign jurisdictions relating to XEN1101 and certain related compounds.

As of December 31, 2018, we have filed a PCT international patent application and have an allowed U.S. non-provisional patent application directed to XEN901 and methods of making and using XEN901 and certain related compounds. Any patents issuing from these applications are expected to expire in 2037 (absent any extensions of term).

As of December 31, 2018, we have filed a PCT international patent application, a U.S. non-provisional patent application and three U.S. provisional patent applications directed to certain of our selective inhibitors of Nav1.6 (exclusive of XEN901), as well as methods of making and using the same. Any patents issuing from these applications are expected to expire between 2037 and 2039 (absent any extensions of term).

As of December 31, 2018, we, together with Genentech, co-owned four issued U.S. patents, seven pending U.S. patent applications, two foreign issued patents (exclusive of European patent national validations) and have filed 43 pending counterpart patent applications in various jurisdictions directed to Nav1.7 inhibitors, as well as methods of making and using the same. The issued patents, as well as any patents issuing from these applications are expected to expire between 2034 and 2037 (absent any extensions of term).

As provided for in our termination agreement with Teva, Teva assigned to us one issued U.S. patent, two pending U.S. patent applications (one of which has since issued as a U.S. patent) and a further two pending PCT international patent applications related to TV-45070 (one of which has since entered national phase in Australia, Canada, China, Europe, Japan, Israel and New Zealand). The issued U.S. patent assigned to us is expected to expire in 2036 (absent any extensions of term) and any patents issuing from the assigned applications are expected to expire in 2037 (absent any extensions of term). For a more detailed description of the terms of our termination agreement with Teva, see "—Collaborations, Commercial and License Agreements" above. Excluding the patents included in the terms of the termination agreement, as of December 31, 2018, we owned five issued U.S. patents related to TV-45070, and methods of making and using TV-45070 and certain related compounds. The issued patents are expected to expire between 2026 and 2033 (absent any extensions of term). In addition, we have nine foreign issued patents (exclusive of European patent national validations) and have filed two pending corresponding foreign applications relating to TV-45070 and certain related compounds.

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 our discovery and product development efforts 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.

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, pre-clinical 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, European Medicines Agency, or EMA, Health Canada 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.

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.

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 product candidates that are in clinical development may compete with various therapies and drugs, both in the marketplace and currently under development.

XEN496, XEN1101, and XEN901 for the Treatment of Epilepsy

If more than one of XEN496, XEN1101, or XEN901 were approved for the treatment of epilepsy, we anticipate that they could potentially compete with each other and other AEDs, which typically can be categorized into four classes by AED mechanism: modulation of voltage-gated ion channels, enhancement of GABA-mediated inhibitory neurotransmission, reduction of glutamate-mediated excitatory neurotransmission, and SV2A modulation. Commonly used AEDs include phenytoin, levetiracetam, carbamazepine, clobazam, lamotrigine, valproate, oxcarbazepine, topiramate, lacosamide, perampanel and cannabidiol. There are currently no FDA-approved treatments specifically indicated for the early infantile epileptic encephalopathies KCNQ2-EE or SCN8A-EE; however, a number of different AEDs are currently used in these patient populations. We are not aware of other companies that are developing selective Nav1.6 inhibitors for the treatment of epilepsy. There are other AEDs in development that could potentially compete with XEN496, XEN1101 or XEN901, including products in development from UCB, Inc., Zogenix, Inc., Sage Therapeutics, Marinus Pharmaceuticals, Inc., Inc., Knopp Biosciences LLC, Upsher-Smith Laboratories, Inc.,

Insys Therapeutics Inc., Supernus Pharmaceuticals Inc., Eisai Co., Ltd., Ovid Therapeutics Inc., Sunovion Pharmaceuticals Inc., and Takeda Pharmaceutical Company Ltd.

Selective Inhibitors of Nav1.7 for the Treatment of Pain

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, gabapentin, and pregabalin. We are also aware of development programs at several pharmaceutical and biotechnology companies that are developing Nav1.7 inhibitors or other sodium channel inhibitors for the treatment of pain, including Amgen Inc., AstraZeneca PLC, Biogen Inc., Bristol-Myers Squibb Company, Dainippon Sumitomo Co., Ltd., Eli Lilly and Company, Merck, NeuroQuest Inc., Newron Pharmaceuticals SpA, Vertex Pharmaceuticals Inc., Voyager Therapeutics, Inc. and Chromocell Corporation in collaboration with its partner Astellas Pharma 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 Nav1.8 inhibitors.

Government Regulation

We are developing small-molecule product candidates, which are regulated as drugs by the FDA and equivalent regulatory authorities outside the U.S. Within the FDA, the Center for Drug Evaluation and Research, or CDER, regulates drugs. Drugs 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. The FD&C Act and 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. FDA approval must be obtained before clinical testing of drugs 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 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.

U.S. Drug Development Process

The process required by the FDA before a drug 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 for marketing approval that includes substantial evidence of safety and efficacy based on large scale phase 3 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 consistently manufacture the product pursuant to regulatory requirements;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the NDA; and
- FDA review and approval of the NDA.

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

- Phase 1. The drug 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 that have the condition or disease being studied.
- Phase 2. The drug 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 a dose range and dosing schedule.
- Phase 3. Clinical studies are undertaken to further evaluate dosing and dosing schedule, clinical efficacy, 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. 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 as well as finalize a process for manufacturing the product in commercial quantities in accordance with GMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other requirements, the sponsor must develop methods for ensuring the quality of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its labeled shelf life.

U.S. Review and Approval Processes

After the completion of clinical studies of a drug, FDA approval of an NDA must be obtained before commercial marketing of the drug. The NDA 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 supplement to an NDA 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 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 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 must be accompanied by a substantial user fee. PDUFA also imposes an annual product fee for drugs and an annual establishment fee on facilities used to manufacture prescription drugs. 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 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 the NDA 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, including additional clinical data. In this event, the NDA 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. The FDA reviews the application to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with GMPs. 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 must submit a proposed REMS; the FDA will not approve the application without a REMS, if required.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the NDA 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, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval will be limited to the specific diseases and dosages studied in clinical trials 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

pursuant to a REMS request, or otherwise limit the scope of any approval.

One of the performance goals agreed to by the FDA under the PDUFA is to complete its review of 90% of standard NDAs within ten months from filing and 90% of priority NDAs 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 the development and review of 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, and may not result in a faster approval, if approval is granted, 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.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug 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 available in the U.S. for this type of disease or condition will be recovered from sales of the product. We have received orphan drug designation from the FDA for XEN007 (active ingredient flunarizine), a drug we are evaluating internally for the potential treatment of HM and AHC. Orphan product designation must be requested before submitting an NDA. 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.

Orphan drug products may also be eligible for RPD designation if greater than 50% of patients living with the disease are under age 19 and the condition affects fewer than 200,000 individuals in the U.S. A priority review voucher will be given to the sponsor of a product with an RPD designation at the time of product approval that is transferable to another company. We have received RPD designation from the FDA for XEN007 for the treatment of AHC. There is no assurance we will receive a RPD priority review voucher or that it will result in a faster development process, review or approval for a subsequent marketing application. Further, it is possible that even if we obtain approval for XEN007 and qualify for such a priority review voucher, the program may no longer be in effect at the time of approval. Although priority review vouchers may be sold or transferred to third parties, there is no guaranty that we will be able to realize any value if we were to sell a priority review voucher.

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 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 designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the EU has similar, but not identical, benefits, including up to ten years of exclusivity.

Post-Approval Requirements

Rigorous and extensive FDA regulation of drug 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 manufacturers, include reporting of GMP deviations that may affect the safety, efficacy or quality 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.

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"), and industry-sponsored scientific and educational activities. 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 manufacturers and other entities involved in the manufacture and distribution of approved drugs 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, 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. 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 whose active ingredient was previously FDA approved, and for which the sponsor is required to generate new clinical data is entitled to three years of market exclusivity. A drug can also obtain pediatric market exclusivity in the U.S. and, 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 timely, voluntary, and as-agreed upon completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

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.

Global Anti-Corruption Laws

The U.S. Foreign Corrupt Practices Act and the Canadian Corruption of Foreign Public Officials Act, the U.S. Travel Act, the OECD Anti-Bribery Convention, Title 18 United States Code section 201, and any other applicable domestic or foreign anti-corruption or anti-bribery laws 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 may also be held liable for the acts of our third party agents under the U.S. Foreign Corrupt Practices Act, Canadian Corruption of Foreign Public Officials Act, and other applicable anti-corruption and anti-bribery laws. Noncompliance with these laws could subject us to investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension or debarment from contracting with certain persons, the loss of export privileges, whistleblower complaints, reputational harm, adverse media coverage, and other collateral consequences. Any investigations, actions or sanctions or other previously mentioned harm could have a material negative effect on our business, operating results and financial condition.

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, research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drugs, and reimbursement requirements. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific for each regulatory authority, submitted for review and approved by the regulatory authority. Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the U.S. have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies. In the EU, for example, a CTA must be submitted to each country’s national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with a country’s requirements, clinical study development may proceed. Similar requirements regarding a CTA and ethics approval exist in Canada.

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. The EU clinical trials legislation currently is undergoing a transition process mainly aimed at harmonizing and streamlining clinical-trial authorization, simplifying adverse-event reporting procedures, improving the supervision of clinical trials and increasing their transparency. Recently enacted Clinical Trials Regulation EU No 536/2014 is intended to ensure that the rules for conducting clinical trials in the EU are identical; however, it has not yet been fully implemented.

To obtain regulatory approval of an investigational drug under EU regulatory systems, we must submit a marketing authorization application, or MAA. The application used to file the NDA in the U.S. is similar to that required in the EU, with the exception of, among other things, country-specific document requirements. Reimbursement approval for the drug by regulatory authorities is also required before a drug may be commercialized. 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.

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 Canada and countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product and establishment licensing, coverage, data protection, 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, inability to import or export, 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 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 or prior authorization of coverage for new or innovative 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.

In addition, in many foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the United States and generally prices tend to be significantly lower.

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 our customers 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.

Enacted in March 2010, the Patient Protection and Affordable Care Act, as amended, or PPACA, is 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. PPACA may continue to place downward pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs.

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

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

The Trump administration and Congress have made changes to current health care laws and may continue to attempt broad sweeping changes to existing health care laws. We face uncertainties that might result from modification or repeal of any of the provisions of the PPACA, including as a result of current and future executive orders and legislative actions. The impact of those changes on us and the pharmaceutical industry as a whole is currently unknown. Any changes to the PPACA are likely to have an impact on our results of operations, and may have a material adverse effect on our result of operations. We cannot predict what other healthcare programs and regulations will ultimately be implemented at the federal or state level or the effect of any future legislation or regulation in the United States may have on our business.

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 that we are developing are subject to regulation by various federal, 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 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 in the U.S. and foreign jurisdictions in which we conduct our business, including jurisdictions in which we conduct our clinical trials. 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 included expansion of HIPAA's privacy and security standards called the Health Information Technology for Economic and Clinical Health Act, or HITECH. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates"—independent contractors or agents of covered entities that create, receive, maintain, or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, in May 2016, the EU formally adopted the General Data Protection Regulation, or GDPR, which applies to all EU member states from May 25, 2018 and replaced the European Union Data Protection Directive. The GDPR has imposed many new or additional requirements including, but not limited to, obtaining consent of the individuals to whom the personal data relates, the nature and scope of notifications provided to the individuals, the security and confidentiality of the personal data, data breach notification and using third party processors in connection with the processing of the personal data. Failure to comply with the GDPR could subject us to regulatory sanctions, delays in clinical trials, criminal prosecution and/or civil fines or penalties. Additionally, GDPR creates a direct cause of action by individual data subjects. The GDPR is a complex law and the regulatory guidance is still evolving, including with respect to how the GDPR should be applied in the context of clinical trials or other transactions from that we may gain access to personal data. These changes in the law will increase our costs of compliance and result in greater legal risks. Other countries maintain different privacy laws that we are subject to.

There are also an increasing number of federal, state and provincial “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, pursuant to a similar federal requirement, manufacturers must 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 U.S. federal government discloses the reported information on a publicly available website. These laws may affect our sales, marketing, and other promotional activities by imposing administrative and compliance burdens on us. If we fail to track and report as required by these laws or otherwise comply with these laws, we could be subject to the penalty provisions of the pertinent state and federal authorities.

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

Environmental Matters

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

Employees

As of December 31, 2018, we had 92 employees, including 89 full-time employees. Of our employees, 57 were primarily engaged in research and development, 24 of whom hold a Ph.D. or M.D. (or equivalent) degree. None of our employees are represented by a labor union. We have not experienced any work stoppages, and we consider our relations with our employees to be good.

Research and Development

We have committed, and expect to continue to commit, significant resources to developing new product candidates. We have assembled an experienced research and development team with scientific and clinical development personnel. Our research and development expenses for the years ended December 31, 2018 and 2017 were $23.6 million and $25.6 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 pre-clinical 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 vary and sourcing adequate supplies may be made more difficult depending on the type of product candidate involved. Our product candidates generally can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. This

chemistry generally is amenable to scale-up and does not require unusual equipment in the manufacturing process.

Corporate Information

We were incorporated in the Province of British Columbia on November 5, 1996 under the predecessor to the Business Corporations Act (British Columbia) under the name “Xenon Bioresearch Inc.” We continued from British Columbia to the federal jurisdiction pursuant to Section 187 of the Canada Business Corporations Act, or the CBCA, on May 17, 2000 and concurrently changed our name to “Xenon Genetics Inc.” We registered as an extra-provincial company in British Columbia on July 10, 2000 and changed our name to “Xenon Pharmaceuticals Inc.” on August 24, 2004. We have one wholly-owned subsidiary as at December 31, 2018, Xenon Pharmaceuticals USA Inc., which was incorporated in Delaware on December 2, 2016. Our principal executive offices are located at 200 – 3650 Gilmore Way, Burnaby, British Columbia, Canada V5G 4W8, and our telephone number is (604) 484-3300. We are a reporting issuer in British Columbia, Alberta and Ontario, but our shares are not listed on any recognized Canadian stock exchange. Our common shares trade on The NASDAQ Global Market under the symbol “XENE.”

Where You Can Find Additional Information

We make available free of charge through our investor relations website, http://investor.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 U.S. Securities and Exchange Commission, or 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 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 a website that contains reports, proxy and information statements, and other information regarding reports that we file or furnish electronically with them at www.sec.gov. Additional information related to Xenon is also available on SEDAR at www.sedar.com.

Item 1A. Risk Factors

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

Risks Related to Our Financial Condition and Capital Requirements

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

We are a clinical stage biotechnology company and, other than the years ended December 31, 2014 and 2013, we have recorded net losses in each annual reporting period since inception in 1996, and we do not expect to have sustained profitability for the foreseeable future. We had net losses of $34.5 million for the year ended December 31, 2018 and an accumulated deficit of $207.9 million as of December 31, 2018, which were driven by expenses incurred in connection with our research and development programs and from general and administrative costs associated with our operations.

We have devoted most of our financial resources to research and development, including our clinical and pre-clinical development activities. To date, we have financed our operations through the sale of equity securities, funding received from our licensees and collaborators, debt financing and, to a lesser extent, government funding. We have not generated any significant revenue from product sales and our product candidates will require substantial additional investment before they may provide us with any revenue.

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

- continue our research and pre-clinical and clinical development of our product candidates;
- expand the scope of our clinical studies for our current and prospective product candidates;
- initiate additional pre-clinical, clinical or other studies for our product candidates;

- change or add additional manufacturers or suppliers and manufacture drug supply and drug product for clinical trials and commercialization;
- 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 or other agreements, including, without limitation, payments to Memorial University of Newfoundland, 1st Order Pharmaceuticals, Inc. and other third parties;
- maintain, protect and expand our intellectual property portfolio;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;

- create additional infrastructure to support our operations 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, Health Canada, 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 significant 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. We have not generated any significant royalty revenue from product sales, and do not otherwise anticipate generating revenue from product sales for the foreseeable future, if ever. If any of our product candidates fail in clinical trials or do not gain regulatory approval, or if any of our future products, if any, once approved, fail to achieve market acceptance or adequate market share, we may never become profitable. Although we were profitable for the years ended December 31, 2014 and 2013, we have not been profitable since that time and may not become profitable 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, pre-clinical and clinical development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete clinical studies;
- commercializing products for which we obtain regulatory and marketing approval, either with a collaborator or, if launched independently, by establishing sales, marketing and distribution infrastructure;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;
- obtaining market acceptance of products for which we obtain regulatory and marketing approval as therapies;
- addressing any competing technological and market developments;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide adequate (in amount and quality) products and services to support clinical development and the market demand for any approved products in the future;
- developing sustainable, scalable, reproducible, and transferable manufacturing processes for any of our products approved in the future;
- maintaining, protecting, expanding and enforcing our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- implementing additional internal systems and infrastructure, as needed; and
- attracting, hiring and retaining qualified personnel.

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 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 the market price of our common shares might be adversely impacted.

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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 pre-clinical 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, potential milestone payments and royalties to third parties, manufacturing of product candidates and products approved for sale, conducting pre-clinical 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, 2018, we incurred approximately $23.6 million of costs associated with research and development, exclusive of costs incurred by our collaborators in developing our product candidates.

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

- the number and characteristics of the future product candidates we pursue either from our internal research efforts or through acquiring or in-licensing other product candidates or technologies;
    - the scope, progress, results and costs of independently researching and developing any of our future product candidates, including conducting pre-clinical research and clinical trials;
    - whether our existing collaborations continue to generate substantial milestone payments and, ultimately, royalties on future approved products for us;
- the timing of, and the costs involved in, obtaining regulatory approvals for any future product candidates we develop independently;
- the timing and magnitude of potential milestone payments and royalties under our product acquisition and in-license agreements;
- the cost of commercializing any future products we develop independently that are approved for sale;
- the cost of manufacturing our future product candidates and products, if any;
- our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such agreements;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patents, including litigation costs and the outcome of such litigation; and
- the timing, receipt and amount of sales of, or royalties on, 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 will enable us to fund our operating expenses and capital expenditure requirements for at least the next 12 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.

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We may allocate our limited resources to pursue a particular drug candidate or indication and fail to capitalize on other drug candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and management resources, we focus on a limited number of research programs and drug candidates. As a result, we may forgo or delay pursuit of opportunities with other drug candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. Our spend on current and future research and development programs and drug candidates for specific indications may not yield any commercially viable drugs. If we do not accurately evaluate the commercial potential or target market for a particular drug candidate, we may relinquish valuable rights to that drug candidate through collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights.

We are party to a loan and security agreement that contains operating and financial covenants that may restrict our business and financing activities and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business.

In December 2017, we entered into a loan and security agreement with Silicon Valley Bank pursuant to which we borrowed an aggregate principal amount of $12 million. In August 2018, we entered into an amended and restated loan and security agreement with Silicon Valley Bank providing for a term loan to us with an aggregate principal amount of $15.5 million, which amount was funded in August 2018. Proceeds from the principal amount borrowed in August 2018 were used in part to refinance the amounts borrowed under the December 2017 loan and security agreement and pay a $0.5 million final payment fee to Silicon Valley Bank in connection with the refinancing of the December 2017 loan and security agreement.

Borrowings under our amended and restated loan and security agreement are secured by substantially all of our assets except intellectual property and subject to certain other exceptions. The loan and security agreement restricts our ability, among other things, to:

- sell, transfer or otherwise dispose of any of our business assets or property, subject to limited exceptions;
- make material changes to our business;
- enter into transactions resulting in significant changes to the voting control of our stock;
- make certain changes to our organizational structure;
- consolidate or merge with other entities or acquire other entities;
- incur additional indebtedness or create encumbrances on our assets;
- pay dividends, other than dividends paid solely in our common shares, or make distributions on and, in certain cases, repurchase our capital stock;
- enter into certain transactions with our affiliates;
- repay subordinated indebtedness; or
- make certain investments.

In addition, we are required under our amended and restated loan agreement and security agreement to comply with various affirmative covenants. The covenants and restrictions and obligations in our amended and restated loan and security agreement, as well as any future financing agreements that we may enter into, may restrict our ability to finance our operations, engage in business activities or expand or fully pursue our business strategies. Our ability to comply with these covenants may be affected by events beyond our control, and we may not be able to meet those covenants. A breach of any of these covenants could result in a default under the amended and restated loan and security agreement, which could cause all of the outstanding indebtedness under the facility to become immediately due and payable.

If we are unable to generate sufficient cash available to repay our debt obligations when they become due and payable, either when they mature, or in the event of a default, we may not be able to obtain additional debt or equity financing on favorable terms, if at all, which may negatively impact our business operations and financial condition.

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 common shares to decline. The sale of additional equity or convertible securities also would dilute all of our shareholders. For example, in May 2018, we entered into a sales agreement with Stifel, Nicolaus & Company, Incorporated, or Stifel, to sell up to $30.0 million of our common shares, from time to time, through an "at-the-market" equity offering program under which Stifel would act as sales agent. We sold an aggregate of 3,440,000 common shares under the May 2018 sales agreement for proceeds of approximately $29.2 million, net of commissions paid, but excluding estimated transaction expenses, before its termination by mutual agreement between us and Stifel in July 2018, in connection with our entry into the July 2018 sales agreement with Jefferies LLC, or Jefferies, and Stifel on the same date. Pursuant to the July 2018 sales agreement, Jefferies and Stifel would act as sales agents to sell our common shares having aggregate gross proceeds of up to $50.0 million. We sold an aggregate of 1,600,000 common shares under the July 2018 sales agreement for proceeds of approximately $14.8 million, net of commissions paid, but excluding estimated transaction expenses, before its termination by mutual agreement between us, Jefferies and Stifel in September 2018. In September 2018, we completed an underwritten public offering of 4,500,000 of our common shares at a public offering price of $14.00 per share for net proceeds of $59.2 million, net of underwriting discounts and commissions, but before other offering expenses. We are also party to an amended and restated loan and security agreement with Silicon Valley Bank pursuant to which we have borrowed an aggregate principal amount of $15.5 million. Our loan pursuant to the amended and restated loan and security agreement is secured by substantially all of our assets except intellectual property and the agreement requires us to comply with various affirmative and negative covenants. The incurrence of additional indebtedness would result in increased fixed payment obligations and, potentially, the imposition of additional restrictive covenants. Such additional covenants could 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 the market price of our common shares could require us to delay or abandon development or commercialization plans. In addition, there is a risk that one or more of our current collaborators, service providers, manufacturers and other partners would not survive or be able to meet their commitments to us under such circumstances, which could directly affect our ability to attain our operating goals on schedule and on budget.

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

As of December 31, 2018, approximately 7% of our cash and cash equivalents and marketable securities were denominated in Canadian dollars. We incur significant expenses in Canadian dollars in connection with our operations in Canada. We do not currently engage in foreign currency hedging arrangements for our Canadian dollar expenditures, and, consequently, foreign currency fluctuations may adversely affect our earnings; however, in the future, we may engage in exchange rate hedging activities in an effort to mitigate the impact of exchange rate fluctuations. 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 market price of our common shares.

Risks Related to Our Business

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

Our clinical product candidates, which include XEN1101 and XEN901, along with clinical product candidates we expect to enter clinical development, which include XEN496 and XEN007, and our pre-clinical compounds, 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 in the market price of our common shares could result.

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, governmental agencies, as well as public and private research institutions. Any product candidates that we or our collaborators successfully develop and commercialize will compete with existing products and any new products that may become available in the future.

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

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, pre-clinical 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, Health Canada 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 the market price of our common shares may suffer.

If XEN496, XEN1101 or XEN901 were approved for the treatment of epilepsy, we anticipate that they could potentially compete with each other and other anti-epileptic drugs, or AEDs. Commonly used AEDs include

phenytoin, levetiracetam, carbamazepine, clobazam, lamotrigine, valproate, oxcarbazepine, topiramate, lacosamide, perampanel and cannabidiol, among others. There are currently no FDA-approved treatments indicated for KCNQ2 epileptic encephalopathy (otherwise known as KCNQ2-EE or EIEE7) or for SCN8A epileptic encephalopathy (otherwise known as SCN8A-EE or EIEE13), an early infantile epileptic encephalopathy due to gain-of-function mutations in the SCN8A gene that encodes the Nav1.6 sodium channel. We are not aware of other companies that are developing selective Nav1.6 inhibitors for the treatment of epilepsy. There are other AEDs in development that could potentially compete with XEN496, XEN1101 or XEN901, including products in development from UCB, Inc., Zogenix, Inc., Sage Therapeutics, Marinus Pharmaceuticals, Inc., SciFluor Lifesciences, Inc., Knopp Biosciences LLC, and Upsher-Smith Laboratories, Inc.

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, gabapentin, and pregabalin. We are also aware of development programs at several pharmaceutical and biotechnology companies that are developing Nav1.7 inhibitors or other sodium channel inhibitors for the treatment of pain, including Amgen Inc., AstraZeneca PLC, Biogen Inc., Bristol-Myers Squibb Company, Dainippon Sumitomo Co., Ltd., Eli Lilly and Company, Merck, NeuroQuest Inc., Newron Pharmaceuticals SpA, Vertex Pharmaceuticals Inc., Voyager Therapeutics, Inc. and Chromocell Corporation in collaboration with its partner Astellas Pharma 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 Nav1.8 inhibitors.

We have no marketed proprietary 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.

As a company, we have no experience in Phase 3 and later stage clinical development, and related regulatory requirements or the commercialization of products. We have not yet demonstrated our ability to independently and repeatedly conduct clinical development after Phase 2, successfully conduct an international multi-center clinical trial, conduct a pivotal clinical trial, obtain regulatory approval, manufacture drug product on a commercial scale or arrange for a third party to do so on our behalf, and commercialize therapeutic products. We will need to develop such abilities if we are to execute on our business strategy to 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 will not be able to develop and commercialize any future product candidates independently and could fail to realize the potential advantages of doing so.

If we are not successful in discovering, acquiring or in-licensing product candidates in addition to XEN496, XEN1101, XEN901, and XEN007, our ability to expand our business and achieve our strategic objectives may be impaired.

We have built a product development pipeline by identifying product candidates either from our internal research efforts or though acquiring or in-licensing other product candidates. To date, our internal discovery efforts have yielded multiple development candidates, including XEN901. Both our internal discovery efforts and our assessment of potential acquisition or in-licensing opportunities require substantial technical, financial and human resources, regardless of whether we identify any viable product candidates.

If we are unable to identify additional product candidates suitable for clinical development and commercialization either from our internal research efforts or though acquiring or in-licensing other product candidates or technologies, 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 the market price of our common shares.

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 approach to drug discovery 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.

Our drug discovery efforts 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 our discovery activities fail 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.

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. Simon Pimstone, our Chief Executive Officer, and Mr. Ian Mortimer, our President and Chief Financial Officer, as well as other employees. The loss of services of either 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, Health Canada and other regulators, provide accurate information to the FDA, EMA, Health Canada and other 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, the General Data Protection Regulation (EU) 2016/679, or GDPR, and the Personal Information Protection and Electronic Documents Act, or PIPEDA, as well as comparable laws in other jurisdictions, may impose obligations with respect to safeguarding the privacy, use, security and transmission of individually identifiable health information such as genetic material or information we have obtained through our direct-to-patient web-based recruitment approach for identifying patients with rare or extreme phenotypes or patients identified for clinical trials.

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,

officers, directors, agents and representatives, including consultants, but it is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent misconduct 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 and 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, exclusion from participation in government healthcare programs, or the curtailment or restructuring of our operations.

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 product candidates for orphan and niche indications. 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.

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

Dr. Simon Pimstone devotes a small amount of his time to clinical work outside of his duties at our company, conducting, generally, one outpatient clinic per week on average. 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 unable 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.

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

Computer system, network or telecommunications failures due to events such as damage from malware, unauthorized access, terrorism, war, or natural disasters could interrupt our internal or partner operations. For example, the loss of pre-clinical trial data, data from completed or ongoing clinical trials for our product candidates or other confidential information could result in delays in our regulatory filings and development efforts, significantly increase our costs and result in other adverse impacts to our business. To the extent that any disruption or cybersecurity breach were to result in a loss of or damage to our data, or inappropriate disclosure of confidential or proprietary information, we could incur liability and other remediation costs, and the development of our product candidates could be delayed. While we have implemented security measures and, to date, have not detected a cybersecurity breach of our systems nor experienced a material system failure, our internal computer systems and the external systems and services used by our third-party contract manufacturers, or CMOs, third-party contract research organizations, or CROs, or other contractors, consultants, directors and partners remain potentially vulnerable to damage from these events.

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

If we engage in significant cross-border and international activities, we will be subject to risks related to international operations, including:

- different regulatory requirements for initiating clinical trials and maintaining approval of drugs 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;
- differing and multiple payor reimbursement regimes, government payors or patient self-pay systems;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations of doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in North America;
- likelihood of potential or actual violations of domestic and international anti-corruption laws, such as the U.S. Foreign Corrupt Practices Act and the U.K. Bribery Act, or of U.S. and international import, export and re-export control and sanctions laws and regulations, which likelihood may increase with an increase of operations in foreign jurisdictions;

- tighter restrictions on privacy and the collection and use of data, including clinical data and genetic material, may apply in jurisdictions outside of North America; 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 common 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 price of our common shares and the composition of our gross income and gross assets, we believe that we may be deemed a PFIC for the taxable years ended December 31, 2018 and 2017, and we could be a PFIC in 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 taxable years ending December 31, 2018 and 2017 or for future taxable years.

If we are a PFIC for any 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. U.S. holders should consult their own tax advisors with respect to their particular circumstances.

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. We will provide upon request, 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 may be a PFIC. U.S. holders should consult their own tax advisors with respect to making this election and the related reporting requirements.

A U.S. holder may also mitigate the adverse tax consequences by timely making a mark-to-market election. Generally, for each year that we 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 common 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. U.S. holders should consult their own tax advisors with respect to the possibility of making this election. In addition, our PFIC status may deter certain U.S. investors from purchasing our common shares, which could have an adverse impact on the market price of our common shares.

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

There is a risk that we may become subject to i