XENON PHARMACEUTICALS INC.

2023 ANNUAL REPORT

April 2024

To Our Shareholders:

Based on the considerable progress made in 2023, we are well positioned to continue to execute on our broad XEN1101 clinical program, which represents the most advanced potassium channel, or Kv7, modulator in clinical development for multiple indications. Importantly, we generated data in our Phase 2 proof-of-concept X-NOVA clinical trial that demonstrated clinically meaningful drug activity in depression, in addition to further supporting XEN1101's highly differentiated profile in epilepsy. With a strong financial position, we are actively planning for late-stage development of XEN1101 in depression and evaluating potential development in additional neurological indications, as we believe this mechanism potentially has broad applicability.

We remain focused on our goal to improve outcomes for epilepsy patients where there continues to be a significant need for new, differentiated anti-seizure medications. The data from our Phase 2b X-TOLE clinical trial in patients with focal onset seizures demonstrated impressive efficacy, with all primary and secondary seizure reduction endpoints reaching statistical significance across all dose groups. The ongoing XEN1101 Phase 2b X-TOLE open label extension study has now collected over six hundred patient years of data, and our interim analyses completed to date have continued to demonstrate compelling efficacy data and seizure freedom rates, while building upon the safety and tolerability profile of XEN1101.

Our Phase 3 X-TOLE2 and X-TOLE3 clinical trials, designed closely after the Phase 2b X-TOLE clinical trial, are evaluating XEN1101 in patients with focal onset seizures. Of the estimated three million adults living with epilepsy in the U.S., approximately 1.8 million adults experience focal onset seizures, and despite the availability of multiple anti-seizure medications, a substantial unmet medical need exists. Also underway, our Phase 3 X-ACKT clinical trial is intended to support potential regulatory submissions in an additional epilepsy indication of primary generalized tonic-clonic seizures, where there also exists a need for new therapeutics.

Based on topline data from our XEN1101 Phase 2 proof-of-concept X-NOVA clinical trial, which demonstrated clinically meaningful drug activity in depression, we are advancing XEN1101 into late-stage development in major depressive disorder. In 2022, approximately 21 million adults were diagnosed with major depressive disorder in the U.S. With its unique mechanism of action, we believe that XEN1101 has the potential to offer a compelling clinical profile for patients with major depressive disorder who are seeking alternatives to the currently available therapeutic options.

In addition to our clinical stage programs, we continue to conduct important pre-clinical work that leverages our expertise in ion channel drug discovery, with a focus on our growing our leadership in the Kv7 space as well as exploring new potential opportunities targeting Nav1.1 for seizure disorders and Nav1.7 for pain.

We are proud of our prudent fiscal management and have established a strong cash position that extends into 2027, allowing us to support the completion of our XEN1101 Phase 3 epilepsy studies and late-stage clinical development of XEN1101 in major depressive disorder.

We want to thank the dedicated directors on our Board and wish to extend our deep gratitude to two of our longest-serving board members – Mohammad Azab and Simon Pimstone – for their service to Xenon over many years. Mohammad served as a Xenon Board member since 2003 while contributing to various Board committees and played a key role in shaping our strategic plan and focus on the late-stage development of XEN1101. As a co-founder of Xenon, it is Simon's vision and drive that has helped position Xenon today as a premier neuroscience company focused on developing and delivering innovative medicines to improve the lives of patients. We have all benefitted immensely from Simon's guidance, leadership, and mentorship, most recently in the role of Board Chair.

We are grateful to all of our employees who are deeply committed to Xenon's mission. There is a sense of excitement and anticipation across the entire Xenon team, as we see the immense opportunity for XEN1101 in epilepsy, depression, and potentially other indications. Further, we believe that our depth of experience in ion channel drug discovery and development will help us continue to advance and grow a robust product pipeline, beyond XEN1101.

Finally, we thank our new and long-term shareholders for their continued support. We intend to build upon the success and the milestone events achieved to date and look forward to sharing updates on our continued progress.

/s/ Ian C. Mortimer

Ian C. Mortimer
President & Chief Executive Officer

/s/ Dawn Svoronos

Dawn Svoronos
Lead Independent Director

Certain statements contained in this letter may constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, Section 21E of the Securities Exchange Act of 1934, as amended, and Canadian securities laws. A detailed discussion of such forward-looking statements and the related risks and uncertainties is included in our Annual Report on Form 10-K included herewith.

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, 2023

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	**V5G 4W8**
(Address of principal executive offices)	**(Zip Code)**

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

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Shares, without par value	XENE	The Nasdaq Stock Market LLC (The Nasdaq Global Market)

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

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

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

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

Indicate by check mark whether the Registrant has submitted electronically 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 whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a 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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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 Global Market on June 30, 2023, was approximately $2,443.4 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 February 26, 2024 was 75,432,482.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Definitive Proxy Statement relating to the 2024 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, 2023.

Auditor Firm Id: 85 Auditor Name: KPMG LLP Auditor Location: Vancouver, BC, Canada

XENON PHARMACEUTICALS INC.

FORM 10-K

For the Fiscal Year Ended December 31, 2023

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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 under applicable law. The words or phrases "would be," "will allow," "intends to," "may," "believe," "plan," "will likely result," "are expected to," "will continue," "is anticipated," "estimate," "project," or similar expressions, or the negative of such words or phrases, are intended to identify "forward-looking statements." You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other "forward-looking" information. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements include, but are not limited to:

- our ability to identify additional products or product candidates either from our internal research efforts or through 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;
- our ability to obtain funding for our operations in sufficient amounts or on terms acceptable to us, including funding necessary to complete further development, approval and, if approved, commercialization of our product candidates;
- our ability to independently develop and commercialize product candidates;
- developments relating to our competitors and our industry, including the success of competing therapies that are or become available;
- our pre-commercial, commercialization, marketing and manufacturing capabilities and strategy;
- our ability to obtain and maintain intellectual property protection for our product candidates and the duration of such protection;
- the therapeutic benefits, effectiveness and safety of our product candidates;
- the timing of, and our and our collaborators' ability to obtain and maintain, regulatory approvals for our product candidates;
- the accuracy of our estimates of the size and characteristics of the markets that may be addressed by our product candidates and our ability to serve those markets, either alone or in partnership with others;
- the rate and degree of market acceptance and clinical utility of any future products;
- the pricing and reimbursement of our product candidates, if approved;
- our expectations regarding federal, state and foreign regulatory requirements;
- our ability to establish and maintain collaborations;
- our expectations regarding macroeconomic and market risk, including interest rate changes and foreign currency fluctuations;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to engage and retain the employees required to grow our business;
- our future financial performance; and
- the direct and indirect impact of public health emergencies on our business and operations, including supply chain, manufacturing, research and development costs, clinical trial conduct, clinical trial data and employees.

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. Other trademarks, trade names or service marks appearing in this Annual Report on Form 10-K belong to their respective holders.

Risk Factors Summary

Our business is subject to numerous risks and uncertainties, including those highlighted in the section of this report captioned "Risk Factors." The following is a summary of the principal risks we face:

- We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.
- We will need to raise additional funding, which may not be available on acceptable terms, if at all. Failure to obtain capital when needed may force us to delay, limit or terminate our product discovery and development programs or commercialization efforts or other operations.
- Our business substantially depends upon the successful development of XEN1101. If we are unable to obtain regulatory approval for, and successfully commercialize, XEN1101, our business may be materially harmed.
- Clinical trials may fail to demonstrate adequately the safety and efficacy of our, or our collaborators', product candidates at any stage of clinical development. Terminating the development of any of our, or our collaborators', product candidates could materially harm our business and the market price of our common shares.
- We, or our collaborators, may find it difficult to enroll patients in our clinical trials which could delay or prevent the successful completion of clinical trials of our product candidates.
- We, or our collaborators, may incur unexpected costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our, or our collaborators', product candidates.
- The regulatory approval processes of the FDA, EMA and regulators in other foreign jurisdictions are lengthy, time-consuming and inherently unpredictable. If we, or our collaborators, are unable to obtain regulatory approval for our product candidates in a timely manner, or at all, our business may be substantially harmed.
- If we are unable to establish our own sales, marketing and distribution capabilities or enter into agreements for these purposes, we may not be successful in independently commercializing any future products.
- Our prospects for successful development and commercialization of our partnered products and product candidates are dependent upon the research, development and marketing efforts of our collaborators.
- Our reliance on third parties to manufacture our product candidates may increase the risk that we will not have sufficient quantities of our product candidates, raw materials, APIs or drug products when needed or at an acceptable cost.
- We rely on third parties to conduct our pre-clinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties, including to comply with applicable laws and regulations or meet expected deadlines, our business could be substantially harmed.
- We could be unsuccessful in obtaining or maintaining adequate patent protection for one or more of our products, product candidates or future products.
- We may not be able to protect our intellectual property rights throughout the world.

- Our business and operations could suffer in the event of an actual or perceived information security incident such as a cybersecurity breach, system failure or other compromise of our systems and/or information, including information held by a third-party contractor or vendor.
- The market price of our common shares may be volatile, and purchasers of our common shares could incur substantial losses.
- Future sales and issuances of our common shares or securities convertible into or exchangeable for common shares would cause our shareholders to incur dilution and could cause the market price of our common shares to fall.

Our Risk Factors are not guarantees that no such conditions exist as of the date of this report and should not be interpreted as an affirmative statement that such risks or conditions have not materialized, in whole or in part.

Item 1. Business

We are a neuroscience-focused biopharmaceutical company committed to improving the lives of people living with neurological and psychiatric disorders. We are advancing a novel product pipeline to address areas of high unmet medical need, including epilepsy and depression. In addition to our proprietary product candidates, we also have partnered programs with academic and industry collaborators, including Neurocrine Biosciences, Inc., or Neurocrine Biosciences.

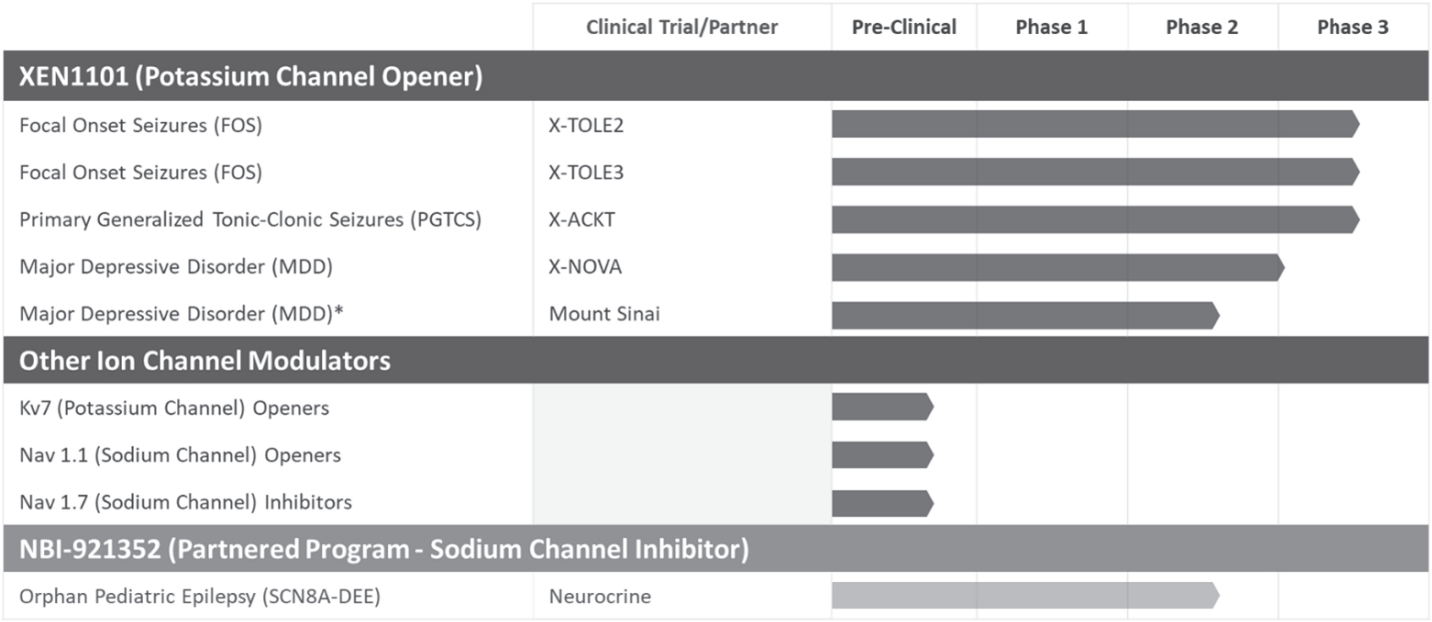
Our Strategy

Our goal is to build a fully-integrated and profitable biopharmaceutical company that discovers, develops, and commercializes innovative therapeutics to treat a range of neuroscience diseases.

Key components of our strategy include:

- Leveraging our discovery capabilities – which were founded upon our understanding of the genetics of channelopathies combined with proprietary biology and medicinal chemistry assets and know-how – to identify product candidates for development, drug targets and/or new indications for our existing product candidates;
- Advancing selected proprietary product candidates through clinical development;
- Selectively establishing collaborations that allow us to potentially expand our internal capabilities and/or address broader commercial opportunities than may be possible independently;
- Identifying opportunities to further expand our pipeline though indication expansion, acquisition, or in-licensing of external product candidates; and
- Commercializing product candidates alone or in collaboration with others.

Our Pipeline



Our Product Candidates

XEN1101

XEN1101 is a novel, potent Kv7 potassium channel opener being developed for the treatment of epilepsy, major depressive disorder, or MDD, and potentially other neurological disorders.

XEN1101 for Epilepsy (Focal Onset Seizures)

Our XEN1101 Phase 3 epilepsy program includes two identical Phase 3 clinical trials, called X-TOLE2 and X-TOLE3, that are designed closely after the Phase 2b X-TOLE clinical trial. These multicenter, randomized, double-blind, placebo-controlled trials are evaluating the clinical efficacy, safety, and tolerability of 15 mg or 25 mg of XEN1101 administered with food as adjunctive treatment in approximately 360 patients per study with focal onset seizures, or FOS. The primary efficacy endpoint is the median percent change, or MPC, in monthly seizure frequency from baseline through the double-blind period, or DBP, of XEN1101 compared to placebo. Xenon anticipates patient enrollment in X-TOLE2 will be completed in late 2024 to early 2025.

XEN1101 for Epilepsy (Primary Generalized Tonic-Clonic Seizures)

Our Phase 3 X-ACKT clinical trial is intended to support potential regulatory submissions in an additional epilepsy indication of primary generalized tonic-clonic seizures, or PGTCS. This multicenter, randomized, double-blind, placebo-controlled study is evaluating the clinical efficacy, safety, and tolerability of 25 mg of XEN1101 administered with food as adjunctive treatment in approximately 160 patients with PGTCS. The primary efficacy endpoint is the MPC in monthly PGTCS frequency from baseline through the DBP of XEN1101 compared to placebo.

XEN1101 for Epilepsy (Open-Label Extension)

Upon completion of the DBP in X-TOLE2, X-TOLE3, or X-ACKT, eligible patients may enter an open-label extension, or OLE, study for up to three years. In addition, the ongoing X-TOLE Phase 2b OLE, which has been extended from five years to seven years, continues to generate important long-term data for XEN1101.

Summary of XEN1101 Clinical Results in Epilepsy

Phase 1: Phase 1 studies conducted in healthy subjects suggested that XEN1101 was generally well tolerated in the doses examined, and its pharmacokinetic profile supported a once-daily dosing schedule with food and without the need for titration, which has been utilized in all Phase 2 and Phase 3 trials. We completed a Phase 1 clinical trial that evaluated the safety, tolerability and pharmacokinetic profile of both single ascending doses, or SAD, and multiple ascending doses, or MAD, of XEN1101 in healthy subjects. 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 majority of adverse events, or AEs, were mild or moderate, resolved spontaneously and were consistent with anti-seizure medications, or ASMs. There were no serious adverse events, deaths, or clinically significant delayed ventricular repolarization or laboratory findings. Phase 1 results suggest that XEN1101 is generally well tolerated in the doses examined (single doses of up to 30 mg and multiple doses of up to 25 mg once daily).

Phase 1b: Data from a Phase 1b transcranial magnetic stimulation, or TMS, study – which was designed to assess XEN1101's ability and potency to modulate cortical excitability – demonstrated activity in the target CNS tissue and helped inform dose selection for our Phase 2b clinical trial. This 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 electroencephalogram, or 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 provided evidence of the CNS effects of a 20 mg dose of XEN1101 as indicated by suppression of cortical and corticospinal excitability, which helped inform dose selection for our XEN1101 Phase 2b clinical trial.

Phase 2b X-TOLE Clinical Trial: In October 2021, we announced topline results from the Phase 2b X-TOLE clinical trial, which was designed as a randomized, double-blind, placebo-controlled, multicenter study to evaluate the clinical efficacy, safety, and tolerability of 10 mg, 20 mg, or 25 mg of XEN1101 administered as once-daily adjunctive treatment with food in adult patients with focal epilepsy. The study included a total of 325 randomized and treated subjects in the safety population and 323 subjects in the modified intent-to-treat population for the efficacy analyses. Subjects had an average age of 40.8 ± 13.3 years, and 8.9%, 40.6%, or 50.5% of the subjects were on and continued taking one, two, or three stable background ASMs throughout the study, respectively, and failed a median of 6 previous ASMs prior to study entry. The median baseline seizure frequency across the study groups was approximately 13.5 seizures per month. Of the 285 subjects who completed the double-blind period, 96.5% entered the OLE to evaluate the long-term safety, tolerability, and effectiveness of XEN1101.

***Summary of X-TOLE Efficacy Results in the DBP*:** The X-TOLE trial met its primary efficacy endpoint with XEN1101 demonstrating a statistically significant and dose-dependent reduction from baseline in monthly (defined as 28 days) focal seizure frequency when compared to placebo (monotonic dose response; $p<0.001$). Primary and secondary measures in the topline data set included a pairwise comparison of each active dose to placebo and a responder analysis with the proportion of patients who achieved a 50% or greater reduction in monthly focal seizure frequency from baseline. XEN1101 demonstrated a statistically significant reduction from baseline in monthly focal seizure frequency in pairwise comparisons to placebo for all three XEN1101 doses. The median percent reduction in monthly focal seizure frequency was 52.8% in the XEN1101 25 mg group, 46.4% in the XEN1101 20 mg group, and 33.2% in the XEN1101 10 mg group compared to 18.2% in the placebo group. Statistical significance was achieved for all dose groups compared to placebo with 2-sided p-values of $p<0.001$ for 25 mg vs. placebo, $p<0.001$ for 20 mg vs. placebo, and $p=0.035$ for 10 mg vs. placebo. A prespecified secondary endpoint of the study was a responder analysis, which compared the proportion of study subjects treated with XEN1101 who achieved a ≥50% reduction in monthly focal seizures versus placebo. The percentage of subjects who achieved a ≥50% reduction in monthly focal seizures was 54.5% in the XEN1101 25 mg group, 43.1% in the XEN1101 20 mg group, and 28.3% in the XEN1101 10 mg group compared to 14.9% in the placebo group. Statistical significance was achieved for all dose groups compared to placebo with 2-sided p-values of $p<0.001$ for 25 mg vs. placebo, $p<0.001$ for 20 mg vs. placebo, and $p=0.037$ for 10 mg vs placebo. In addition to the topline data, further sub-analyses were presented in December 2021 at the Annual Meeting of the American Epilepsy Society, or AES 2021. These sub-analyses include the proportion of patients with at least a 75% reduction in monthly focal seizure frequency from baseline along with the proportion of patients who achieved 100% reduction in monthly seizure frequency from baseline. Efficacy results are summarized in the following table; all p-values are 2-sided comparing the active dose to placebo for the prespecified primary and secondary seizure reduction endpoints:

	XEN1101 25 mg (N=112)	XEN1101 20 mg (N=51)	XEN1101 10 mg (N=46)	Placebo (N=114)
Median reduction from baseline in monthly focal seizure frequency	52.8% (p<0.001)	46.4% (p<0.001)	33.2% (p=0.035)	18.2%
Patients with **at least a 50%** reduction in monthly focal seizure frequency from baseline	54.5% (p<0.001)	43.1% (p<0.001)	28.3% (p=0.037)	14.9%
Patients with **at least a 75%** reduction in monthly focal seizure frequency from baseline	29.5%	29.4%	8.7%	6.1%
Patients with **100%** reduction in monthly focal seizure frequency from baseline	6.3%	7.8%	2.2%	1.8%

Additional sub-analyses were performed in patients with different baseline characteristics given that X-TOLE included a difficult-to-treat patient population as defined by the number of prior failed ASMs, concomitant ASMs on study, and baseline seizure burden. The table below outlines a sub-group analyses of median percent reduction in seizures within the 25 mg dose group, showing that there was a significant increase in seizure reduction in patients with less disease severity at baseline:

	XEN1101 25 mg Median reduction from baseline in monthly focal seizures frequency	Placebo
Overall in X-TOLE	52.8% (N=112)	18.2% (n=114)
Prior failed ASMs > 6	43.2% (n=45)	14.2% (n=47)
Prior failed ASMs ≤ 6	58.3% (n=67)	20.5% (n=67)
Concomitant ASMs = 3	51.3% (n=54)	20.4% (n=56)
Concomitant ASMs ≤ 2	59.7% (n=58)	14.4% (n=58)
Baseline seizures > 8.5 per month	50.8% (n=83)	18.2% (n=84)
Baseline seizures ≤ 8.5 per month	70.6% (n=29)	18.8% (n=30)

In addition, an analysis of seizure reduction across seizure subtypes showed a median percent reduction in monthly focal seizure frequency of 86.9% (n=23) in 'type 4' focal seizures that lead to generalized tonic clonic seizures in the 25 mg dose group. A time-to-event analysis analyzing the time to reach the baseline monthly focal seizure count during the double-blind period showed a marked dose-dependent decrease in the rate of seizure recurrence when comparing XEN1101 to placebo.

These marked reductions in seizures were associated with statistically significant improvements in overall status, as assessed by physicians using the Clinical Global Impression of Change, or CGI-C, and by subject self-reporting using the Patient Global Impression of Change, or PGI-C, scales in the XEN1101 25 mg group, which are shown in the table below:

	XEN1101 25 mg (N=112)	Placebo (N=114)
CGI-C (Portion of patients much improved or very much improved)	46.4% (p<0.001)	22.8%
PGI-C (Portion of patients much improved or very much improved)	42.9% (p=0.001)	21.9%

The XEN1101 25 mg group was statistically significant in CGI-C and PGI-C, and the XEN1101 20 mg group was statistically significant in PGI-C, while the XEN1101 20 mg group in CGI-C and the XEN1101 10 mg group for both CGI-C and PGI-C showed numerical improvements over placebo but were not statistically significant.

***Summary of X-TOLE Safety Results in the DBP*:** XEN1101 was generally well-tolerated in the DBP with AEs consistent with other ASMs. The incidence of treatment-emergent adverse events, or TEAEs, was higher in the treatment groups as compared to the placebo group, with 62.3% of patients in the placebo group, 67.4% of patients in the XEN1101 10 mg group, 68.6% of patients in the XEN1101 20 mg group, and 85.1% of patients in the XEN1101 25 mg group experiencing at least one TEAE. The TEAEs that were greater than or equal to 5% in all treatment arms were attributed to nervous system disorders; psychiatric disorders; general disorders; gastrointestinal disorders; eye disorders; and infections – with the majority related to the central nervous system, mild or moderate in severity, and occurring early in the treatment period. Across all XEN1101 dose groups (n=211), the most common TEAEs were dizziness (n=52, 24.6%), somnolence (n=33, 15.6%), fatigue (n=23, 10.9%), and headache (n=21, 10.0%). The breakdown of subjects with dizziness across dose groups including placebo is as follows: 8 subjects (7.0%) in the placebo group, 3 subjects (6.5%) in the 10 mg group, 13 subjects (25.5%) in the 20 mg group, and 36 subjects (31.6%) in the 25 mg group. The incidence of treatment-emergent serious adverse events, or SAEs, was similar in all four arms of the study with 2.6% of patients in the placebo group, 4.3% of patients in the XEN1101 10 mg group, 3.9% of patients in the XEN1101 20 mg group, and 2.6% of patients in the XEN1101 25 mg group experiencing at least one treatment-emergent SAE. There were 3.5% of subjects in the placebo group, 2.2% of subjects in the XEN1101 10 mg group, 13.7% of subjects in the XEN1101 20 mg group, and 15.8% of subjects in the XEN1101 25 mg group that had an AE leading to treatment discontinuation. Two TEAEs of urinary retention were reported in the active treatment groups, one of which required a dose reduction, and both subjects remained on drug with no other changes or intervention. There was no evidence of urinary retention based upon mean differences across treatment groups in the total or individual items of the American Urological Association Symptom Index. There was no cardiovascular signal of concern based on vital signs from resting or orthostatic tests; there were no safety signals of concern from physical or neurologic exams; and there were no signals of concern from ECGs, safety labs or urinalysis. Weight changes were modest with mean (SD) changes of 0.2 kg (2.4) in the placebo group, 0.6 kg (2.3) in the 10 mg group, 1.6 kg (2.2) in the 20 mg group and 1.9 kg (2.9) in the 25 mg group.

Additional Post Hoc Sub-Analyses of X-TOLE Data and Interim Open Label Extension (OLE) Data: In 2022 and 2023, we presented additional sub-group analyses of data from the XEN1101 Phase 2b X-TOLE clinical trial and interim data from the ongoing X-TOLE OLE.

Additional sub-analyses of the X-TOLE data suggest that the rapid onset of efficacy for XEN1101 was associated with starting at an effective, therapeutic dose. There was a statistically significant reduction in median seizure frequency within one week for all doses compared with placebo. Rapid onset of efficacy of XEN1101 was seen at week 1, with a dose-dependent reduction from baseline in median weekly seizure frequency of 39.1% ($p<0.01$, n=46), 41.5% ($p=0.04$, n=50) and 55.4% ($p<0.001$, n=110) in the 10 mg, 20 mg, and 25 mg groups, respectively, compared to placebo (20.2%, n=114).

Analyses of the interim OLE data show XEN1101 continues to be generally well-tolerated, yielding long-term efficacy at the 20 mg once-daily dose, with 60% retention at 24 months in the OLE, as of the analysis cutoff date of September 5, 2023. During OLE study months 18 to 30, there was a sustained monthly reduction in seizure frequency (78%–95% median percent change) from double-blind period baseline, and higher reductions were observed for patients who were receiving one to two ASMs at baseline compared to those receiving three ASMs. Seizure freedom for ≥3-month, ≥6-month, and ≥12-month consecutive durations was achieved in 37.5%, 22.2%, and 14.9% of all patients enrolled in the OLE (n=275), respectively. Seizure freedom for ≥3-month, ≥6-month, and ≥12-month consecutive durations was achieved in 56.4%, 34.5% and 23.6% of those patients with at least 24 months of treatment in the OLE (n=165), respectively. At 24 months in the OLE, clinically important improvements in the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) subscales of Seizure Worry, Social Functioning, and Medication Effects were seen across all patients (n=162), with even greater improvements in the seizure-free group (n=39). In addition, quality-of-life improvements, as measured by the QOLIE-31, originally reported at year one were maintained or improved at year two of the X-TOLE OLE. No new safety signals were identified, and the clinical data analyzed to date indicates that XEN1101 continues to be generally well-tolerated in the OLE with AEs consistent with prior results and AEs seen with other anti-seizure medications. Based on the potential to continue to provide significant benefit to patients, we have extended the X-TOLE OLE from five to seven years.

About Epilepsy and Seizure Types

Epilepsy is a chronic neurologic disorder, the hallmark of which is recurrent, unprovoked and unpredictable seizures. Individuals are diagnosed with epilepsy if they have two unprovoked seizures (or one unprovoked seizure with the likelihood of recurrent seizures) that were not caused by a known and reversible medical condition. Seizures are generally described in two major groups: focal onset seizures, or FOS, and generalized onset seizures. FOS are the most common type of seizure experienced by people with epilepsy. FOS are localized within the brain and can either stay localized or spread to the entire brain, which is typically categorized as a secondarily generalized seizure. FOS account for approximately 60% of seizures in the U.S., which results in a total FOS patient population of approximately 1.8 million patients. Generalized onset seizures affect both sides of the brain or groups of cells on both sides of the brain at the same time. This term includes primary generalized tonic-clonic seizures, or PGTCS, absence seizures, and atonic seizures. Generalized onset seizures account for approximately 30% of seizures in the U.S., or approximately 0.9 million patients, of which the majority experience PGTCS. The remaining 10% of seizures in the U.S. are characterized as unknown onset seizures, which occurs when the beginning of the seizure is unknown. As more information is learned, unknown onset seizures may later be diagnosed as focal onset or generalized onset seizures.

Numerous ASMs are available for the treatment of seizures in the U.S., although there are fewer indicated for PGTCS. The treatment of an individual patient with FOS or PGTCS is currently focused on reduction of seizure frequency, with seizure freedom as the ultimate goal. Early treatment typically begins with monotherapy followed by increasing use of polypharmacy to manage patients with residual seizure burden. Despite the availability of multiple treatment options, up to 50% of patients are considered inadequately managed with initial lines of therapy warranting additional treatment options. For poorly managed patients, physicians increasingly turn to complementary mechanisms used as adjunctive therapy to control seizures. We believe there is a need for new, more effective and tolerable treatments for FOS and PGTCS that have rapid onset of action, unique mechanisms important in polypharmacy, are easy to take (for example, once-daily), and durable. Based on our market research, we believe XEN1101 could offer a compelling value proposition to address FOS and PGTCS, if approved.

XEN1101 for Major Depressive Disorder (MDD)

In November 2023, we reported topline results from the randomized, double-blind, placebo-controlled, Phase 2 proof-of-concept X-NOVA clinical trial, which evaluated the clinical efficacy, safety, and tolerability of 10 mg and 20 mg of XEN1101 taken once daily with food in 168 patients with moderate to severe major depressive disorder, or MDD. The primary objective was to assess the efficacy of XEN1101 compared to placebo on improvement of depressive symptoms in subjects diagnosed with moderate to severe MDD, using the Montgomery-Åsberg Depression Rating Scale, or MADRS, score change through week 6.

We anticipate participating in an "end-of-Phase 2" meeting with the U.S. Food and Drug Administration, or FDA, in April 2024 to support the initiation of our late-stage XEN1101 clinical program in MDD, which will include three Phase 3 clinical trials, with the first Phase 3 study expected to begin in the second half of 2024. We are also evaluating other potential indications for the future development of XEN1101.

Summary of X-NOVA Efficacy Data in the DBP: The primary endpoint of the study was a change in MADRS at week 6. The mean reduction was 13.90 in the placebo group, 15.61 in the XEN1101 10 mg group and 16.94 in the XEN1101 20 mg group. A clear dose response and a clinically meaningful, but not statistically significant, 3.04 difference between placebo and the XEN1101 20 mg group ($p=0.135$) was observed. Statistical significance was achieved on the pre-specified endpoint of the Hamilton Depression Rating Scale, or HAM-D17, at week 6 with a mean reduction of 10.18 in the placebo group and 13.26 in the XEN1101 20 mg group ($p=0.042$). Statistical significance was achieved on the key secondary endpoint of a change in the Snaith-Hamilton Pleasure Scale, or SHAPS, measuring anhedonia at week 6 with a reduction of 5.30 in the placebo group and 7.77 in the XEN1101 20 mg group ($p=0.046$). Statistical significance was achieved in MADRS at week 1 with a mean reduction of 4.88 in the placebo group and 7.54 in the XEN1101 20 mg group ($p=0.047$) demonstrating early onset of efficacy. Statistical significance was achieved in reporting of at least minimally improved symptoms of depression as assessed by physicians using the Clinical Global Impression of Improvement, or CGI-I, ($p=0.004$) in the XEN1101 20 mg group compared to placebo.

Summary of X-NOVA Safety and Tolerability Data in the DBP: XEN1101 was well tolerated with similar rates of adverse events reported across all treatment arms. The most commonly reported TEAEs in the XEN1101 20 mg group included dizziness (17.9%), somnolence (10.7%), headache (8.9%) and disturbance in attention (8.9%), as compared to the placebo group which reported dizziness (7.3%), somnolence (1.8%), headache (12.7%) and disturbance in attention (0%). Rates of discontinuation were similar across all treatment arms and rates of discontinuation due to TEAEs were low with three patients in the XEN1101 20 mg group (5.4%), as compared to two patients in the placebo group (3.6%). No serious adverse events, or SAEs, were reported in the two XEN1101 treatment groups and there were two patients (3.6%) in the placebo group who experienced a treatment-emergent SAE. XEN1101 was not associated with notable weight gain, and patients did not report notable sexual dysfunction.

Investigator-Led Phase 2 Proof-of-Concept Study of XEN1101 in MDD

We are also collaborating with the Icahn School of Medicine at Mount Sinai to support an ongoing investigator-sponsored Phase 2 proof-of-concept, randomized, parallel-arm, placebo-controlled multi-site study of XEN1101 for the treatment of MDD in approximately 60 subjects. The primary objective of the study is to investigate the effect of XEN1101 on the brain reward circuit as measured by the change in bilateral ventral striatum activity as assessed by functional MRI, or fMRI. The secondary objectives are to test the effect of XEN1101 compared to placebo on clinical measures of depression and anhedonia using the MADRS and SHAPS, respectively.

About Major Depressive Disorder (MDD)

MDD is a common, chronic neurological disorder characterized by low mood, inability to feel pleasure, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms that last for two weeks or more, and which impairs social, occupational, educational, or other important functioning. MDD is highly prevalent and difficult to treat. According to the National Institutes of Health, an estimated 7.8% of U.S. adults (21.0 million) experience MDD each year, and of them approximately two-thirds had severe impairment associated with their depression. Results of the Sequenced Treatment Alternatives to Relieve Depression, or STAR*D trial, funded by the National Institute of Mental Health, indicate that nearly two-thirds of diagnosed and treated patients do not experience adequate treatment response with first-line therapy, and that the majority of these initial failures also fail second-line treatment, highlighting the need for new anti-depressant medications with novel mechanisms of action.

Intellectual Property Related to XEN1101

We have a comprehensive strategy in place to protect and expand the intellectual property portfolio that covers XEN1101. Importantly, two U.S. patents were issued in 2021 with claims covering: (1) distinct crystalline forms of XEN1101 drug substance and related pharmaceutical compositions, along with methods for their preparation and use; and (2) various methods of orally administering XEN1101 with or close to a meal. These U.S. patents are expected to expire in 2040 and 2039, respectively, absent any extensions of patent term. For a more detailed description of our intellectual property portfolio covering our pipeline of product candidates, see "—Intellectual Property" below.

New Pipeline Opportunities

Given our expertise in drug discovery, our efforts are concentrated on the identification of ion channel targets where we believe novel modulators might represent significant therapeutic advances. Expansion of our pipeline may come from our internal research efforts and through the acquisition or in-licensing of other external product candidates. The near-term focus is on internal development candidates targeting Kv7, Nav1.1 and Nav1.7. Additional updates will be provided as these pre-clinical drug candidates advance into clinical development.

Our Partnered Programs

NBI-921352, A Clinical Stage, Selective Nav1.6 Sodium Channel Inhibitor for the Treatment of Epilepsy

In December 2019, we entered into a license and collaboration agreement with Neurocrine Biosciences to develop treatments for epilepsy. Neurocrine Biosciences has an exclusive license to XEN901, now known as NBI-921352, a clinical stage selective Nav1.6 sodium channel inhibitor, and an exclusive license to pre-clinical compounds for development, including selective Nav1.6 inhibitors and dual Nav1.2/1.6 inhibitors. The agreement also included a multi-year research collaboration to discover, identify and develop additional novel Nav1.6 and Nav1.2/1.6 inhibitors, which was completed in June 2022. Pursuant to the terms of the agreement, we have the potential to receive certain clinical, regulatory, and commercial milestone payments, as well as future sales royalties. For a more detailed description of the terms of this agreement with Neurocrine Biosciences, see "—Collaborations, Commercial and License Agreements" below.

NBI-921352 is being developed to treat pediatric patients with SCN8A developmental and epileptic encephalopathy, or SCN8A-DEE. A Phase 2 clinical trial is underway evaluating NBI-921352 in pediatric patients (aged between 2 and 21 years) with SCN8A-DEE. Neurocrine Biosciences has received orphan drug and rare pediatric disease designations from the FDA for NBI-921352 in SCN8A-DEE.

In November 2023, Neurocrine Biosciences reported that a Phase 2 clinical trial evaluating NBI-921352 in adult patients with FOS failed to demonstrate meaningful reduction in seizure frequency and that no further development with NBI-921352 in FOS is planned at this time.

Collaborations, Commercial and License Agreements

License and Collaboration Agreement with Neurocrine Biosciences, Inc.

In December 2019, as amended in January 2021 and February 2022, we entered into a license and collaboration agreement, or the Collaboration Agreement, with Neurocrine Biosciences to establish a collaboration under which the parties will identify, research and develop sodium channel inhibitors, including our clinical candidate XEN901, now known as NBI-921352, and certain preclinical candidates ("DTCs") and research compounds which Neurocrine Biosciences will have the exclusive right to further develop and commercialize under the terms and conditions set forth in the Collaboration Agreement.

Neurocrine Biosciences has an exclusive, royalty-bearing, sublicensable license to certain of our intellectual property rights for the research, development and commercialization of these compounds on a worldwide basis for the treatment, cure, diagnosis, prediction or prevention of any human disease or disorder, state, condition and/or malady, subject to certain exceptions set forth in the Collaboration Agreement. We also granted to Neurocrine Biosciences a non-exclusive, non-royalty-bearing, sublicensable license to certain of our intellectual property rights for the screening of compounds for identification as a Select Nav Inhibitor (as defined below) and for the research of certain compounds otherwise expressly excluded from the Collaboration Agreement, or the Excluded Compounds.

During the term of the Collaboration Agreement, other than the Excluded Compounds and otherwise in accordance with the terms of the Collaboration Agreement, neither we nor any of our respective affiliates are permitted to directly or indirectly research, develop, manufacture or commercialize a compound that, as its primary mechanism of action, binds to and inhibits voltage-gated sodium channels Nav1.2 and Nav1.6, such compound referred to as a Select Nav Inhibitor.

Each party is solely responsible for all costs such party incurs to conduct its activities under the development and research plans, provided that, with respect to NBI-921352 development and research activities, Neurocrine Biosciences reimburses us for certain full-time employees and out-of-pocket expenses incurred by us, and with respect to certain development activities related to certain DTCs, Neurocrine Biosciences may make agreed-upon reimbursements.

Except for the activities set forth in the development plans, Neurocrine Biosciences is solely responsible, at its sole cost and expense, for all development and manufacturing of the compounds and any pharmaceutical product that contains a compound, subject to the Co-Funding Option (as defined below). We will have the right to elect to co-fund the development of one product in the first indication that meets or exceeds a specified prevalence threshold, or a Major Indication, under such development plan and to receive a mid-single digit percentage increase in royalties owed on the net sales as calculated pursuant to the terms of the Collaboration Agreement, or Net Sales, of such products in the U.S., or the Co-Funding Option. If we exercise the Co-Funding Option, the parties will share equally all reasonable and documented costs and expenses that Neurocrine Biosciences incurs in connection with the development of such product in the applicable indication, except costs and expenses that are solely related to the development of such product for regulatory approval outside the U.S. We have not exercised this option as of December 31, 2023.

Neurocrine Biosciences paid us an upfront payment of $50.0 million, which included a $30.0 million payment in cash. For the remainder of the upfront payment, concurrently with the entry into the Collaboration Agreement, the parties entered into the Share Purchase Agreement (as defined below) pursuant to which we issued and sold the Shares (as defined below) to Neurocrine Biosciences for an aggregate purchase price of $20.0 million.

Based on the regulatory approval of a clinical trial application in Europe for NBI-921352 for focal-onset seizures in adults, in September 2021 we received an aggregate milestone payment of $10.0 million in the form of $4.5 million in cash and a $5.5 million in equity investment. In January 2022, we received an aggregate milestone payment of $15.0 million in the form of a $6.75 million payment in cash and a $8.25 million equity investment, based on the FDA's acceptance of a protocol amendment to expand the study population of a clinical trial in pediatric patients with SCN8A-DEE.

The Collaboration Agreement also provides for potential aggregate development and regulatory milestone payments from Neurocrine Biosciences to us of up to $325.0 million for a NBI-921352 product and up to $247.5 million for each other Compound up to a maximum of three other Compounds. Sales-based milestones of up to $150.0 million for each Compound, including a NBI-921352 product, will be paid from Neurocrine Biosciences to us upon the achievement of certain Net Sales targets, up to a maximum of four Compounds.

Neurocrine Biosciences' obligations to pay royalties with respect to a product and country will expire upon the latest of: (i) the expiration of the last to expire valid claim in (a) the parties' joint patent rights filed during the Research Term or a specified period of time thereafter or (b) our patent rights as specified in the Collaboration Agreement, in each case that cover such product; (ii) ten years from the first commercial sale of the product in such country; and (iii) the expiration of regulatory exclusivity for such product in such country, or the Royalty Term. Royalty payments are subject to reduction in specified circumstances, including expiration of patent rights or if average Net Sales decrease by a certain percentage after the introduction of a generic product. Unless earlier terminated, the term of the Collaboration Agreement will continue on a product-by-product and country-by-country basis until the expiration of the Royalty Term for such product in such country.

Neurocrine Biosciences may terminate the Collaboration Agreement in its entirety or on a product-by-product or country-by-country basis, for any or no reason, by providing at least 90 days' written notice, provided that such unilateral termination will not be effective (i) with respect to a NBI-921352 product until Neurocrine Biosciences has used its commercially reasonable efforts to complete one Phase 2 clinical trial for a NBI-921352 product; (ii) with respect to a DTC product until Neurocrine Biosciences has used its commercially reasonable efforts to complete one Phase 1 clinical trial for a DTC product; and (iii) with respect to the Collaboration Agreement in its entirety until Neurocrine Biosciences has used its commercially reasonable efforts to complete both of these clinical trials. Either party may terminate the Collaboration Agreement in the event of a material breach in whole or in part, subject to specified conditions. If Neurocrine Biosciences is entitled to terminate the Collaboration Agreement due to our uncured material breach, in lieu of termination, Neurocrine Biosciences may elect to reduce all subsequent payments owing from Neurocrine Biosciences to us by half.

Upon the termination of the Collaboration Agreement for any reason, all licenses and other rights granted to Neurocrine Biosciences by us shall terminate, provided that if termination is solely with respect to one or more products or countries, then such termination will apply only to the terminated products or countries. Upon termination in certain cases, Neurocrine Biosciences has agreed to grant us licenses to certain Neurocrine Biosciences intellectual property that is reasonably necessary, and that was actually used by Neurocrine Biosciences for the development, manufacturing or commercialization of the terminated products, to research, develop and commercialize the terminated products in the terminated countries. Such license will be royalty-free with respect to any terminated product for which a Phase 2 clinical trial was not completed prior to the effective date of termination, and otherwise will be royalty-bearing ranging from a low-single digit percentage to a high-single digit percentage depending on the stage of development of the applicable product at the effective date of termination.

Share Purchase Agreements

On December 2, 2019, pursuant to the Collaboration Agreement, we entered into a Share Purchase Agreement, or SPA, with Neurocrine Biosciences pursuant to which we issued and sold 1,408,847 of our common shares, or Shares, to Neurocrine Biosciences in a private placement for an aggregate purchase price of $20.0 million, or $14.196 per share. The purchase price represented a 20% premium to the closing price of our common shares on November 29, 2019.

We entered into additional SPAs in September 2021 and January 2022 with Neurocrine Biosciences pursuant to which we issued and sold 275,337 and 258,986, respectively, of our Shares to Neurocrine Biosciences in private placements for aggregate purchase prices of $5.5 million ($19.9755 per share) and $8.25 million ($31.855 per share), respectively. The purchase price represented a 15% premium to our 30-day volume-weighted average price immediately prior to the public announcements.

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.

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.

In August 2020, we entered into an amendment to the asset purchase agreement to amend certain definitions in the agreement and to modify the payment schedule for certain milestones. Upon execution of the amendment, we made a payment of $0.3 million to 1st Order. In February 2023, an additional $1.4 million was paid for the achievement of clinical and other milestones. We remain responsible for future potential payments of up to $6.0 million in regulatory milestones. There are no royalty obligations to 1st Order.

Intellectual Property

As part of our business strategy, we strive to protect the proprietary technologies that we believe are important to our business, including pursuing and maintaining patent protection intended to cover our product candidates and their methods of use and processes for their manufacture, as well as other inventions that are important to our business. We plan to continue to expand our intellectual property estate by filing patent applications directed to compositions, methods of use, treatment and patient selection, formulations and manufacturing processes created or identified from our ongoing development of our product candidates and future products. 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, 2023, we owned, co-owned or licensed 16 U.S. issued patents and 56 patents in foreign jurisdictions (exclusive of European patent national validations), and over 370 pending patent applications.

With regard to XEN1101, as of December 31, 2023, we owned 4 U.S. issued patents, 29 issued patents in foreign jurisdictions (exclusive of European patent national validations) and over 200 pending patent applications. The issued patents, along with any patents issuing from these applications, are expected to expire between 2028 and 2044 (absent any extensions of term).

With regard to NBI-921352 (formerly known as XEN901), as of December 31, 2023, we owned or co-owned 4 U.S. issued patents, 12 issued patents in foreign jurisdictions (exclusive of European patent national validations), and over 18 pending patent applications. The issued patents, along with any patents issuing from these applications, are expected to expire between 2037 and 2044 (absent any extensions of term). With regard to our selective inhibitors of Nav1.6 and/or Nav1.2 (exclusive of NBI-921352), as of December 31, 2023, we owned 6 U.S. issued patents, 15 issued patents in foreign jurisdictions (exclusive of European patent national validations), and over 90 pending patent applications. The issued patents, along with any patents issuing from these applications, are expected to expire between 2037 and 2039 (absent any extensions of term). Pursuant to our collaboration with Neurocrine Biosciences, Neurocrine Biosciences controls the prosecution, maintenance and other matters relating to the patent portfolio for NBI-921352 and the other selective Nav1.6 inhibitors and dual Nav1.2/1.6 inhibitors, although we have a right to comment.

With regard to our development programs, including targets related to Kv7 (exclusive of XEN1101), Nav1.1 and Nav1.7, as of December 31, 2023, we owned 1 U.S. issued patent and over 20 pending patent applications. The issued patents, along with any patents issuing from these applications, are expected to expire between 2036 and 2044 (absent any extensions of term).

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 candidate 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, or other foreign 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.

If one or more of our proprietary or partnered product candidates were approved for the treatment of epilepsy, we anticipate that they could potentially compete with other ASMs or one another. These currently commonly prescribed ASMs, among others, include brivaracetam, carbamazepine, cenobamate, clobazam, eslicarbazepine acetate, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenytoin, topiramate, and valproate. There are other ASMs in development that could potentially compete with our products, including product candidates in development from Biohaven Ltd., Cerevel Therapeutics Holdings, Inc., Equilibre Biopharmaceuticals Corp., Johnson & Johnson Innovative Medicine, Neurona Therapeutics Inc., Praxis Precision Medicines, Inc., Rapport Therapeutics, Inc., SK Life Science Inc., Supernus Pharmaceuticals, Inc., and Zhimeng Biopharma, Inc. If one or more of our proprietary product candidates were approved for the treatment of MDD, we anticipate that they could potentially compete with other anti-depressant medications, or ADs. Patients with MDD are typically treated with a variety of ADs, which include selective serotonin reuptake inhibitors, or SSRIs, benzodiazepines, serotonin / norepinephrine reuptake inhibitors, or SNRIs, norepinephrine and dopamine reuptake inhibitors, or NDRIs, N-methyl-D-aspartate, or NMDA, receptor agonists and atypical antipsychotics. Currently prescribed antidepressants include benzodiazepines, brexpiprazole, bupropion, bupropion/dextromethorphan, cariprazine, citalopram, duloxetine, escitalopram, esketamine, fluoxetine, ketamine, sertraline, trazodone, tricyclic agents, venlafaxine, vilazodone and vortioxetine. We are aware of several companies developing product candidates for the treatment of MDD including AbbVie Inc., Biohaven Ltd., Intra-Cellular Therapies, Inc., Johnson & Johnson Innovative Medicine, Neumora Therapeutics, Inc., Relmada Therapeutics, Inc., Sage Therapeutics, Inc. and Sumitomo Pharma America, Inc.

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 of an investigational new drug application, or IND, must be obtained before clinical testing of drugs is initiated, and each clinical study protocol for such product candidates is reviewed by the FDA and an institutional review board, or IRB, 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. Failure to comply with the applicable U.S. regulatory requirements at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions. These sanctions could include, among other actions, FDA's refusal to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters and other types of enforcement-related letters, product recalls, product seizures, relabeling or repackaging, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by FDA and the Department of Justice or other governmental entities.

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 and 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, which is usually based on large-scale Phase 3 clinical studies;
- satisfactory completion of an FDA pre-approval 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 inspection of the nonclinical and clinical study sites that generated the data in support of the NDA; and
- payment of applicable user fees and FDA review and approval of the NDA.

The data required to support an NDA is generated in two distinct development stages: pre-clinical and clinical. For new chemical entities, the pre-clinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, evaluating purity and stability, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. The conduct of the pre-clinical tests must comply with federal regulations, including GLPs and the U.S. Department of Agriculture's Animal Welfare Act. The sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Some long-term pre-clinical testing, such as animal tests of reproductive AEs and carcinogenicity, may continue after the IND is submitted. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, submission of an IND does not guarantee the FDA will allow clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

If the FDA accepts the IND, the drug can then be studied in human clinical trials to determine if the drug is safe and effective. The clinical stage of development involves the administration of the drug product to human subjects, including patients, under the supervision of qualified investigators in accordance with GCPs, which establish standards for conducting, recording data from, and reporting the results of clinical trials, and also include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial.

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. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA. 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, identity, strength and purity of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug does not undergo unacceptable deterioration over its labeled shelf life.

Further, due to disasters and public health emergencies, we may be required to develop and implement additional clinical trial policies and procedures designed to help protect subjects. For example, the FDA has issued guidance on conducting clinical trials during major disruptions due to disasters and public health emergencies, which describes a number of considerations for sponsors of clinical trials impacted by these events, to ensure the safety of trial participants, maintaining GCP compliance, and minimizing risks to trial integrity. We may be required to make further adjustments to our clinical trials or business operations based on current or future guidance and regulatory requirements as a result of major disruptions due to disasters and public health emergencies.

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 can begin. 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, which typically describes all of the specific deficiencies in the application identified by the FDA. The deficiencies identified may be minor (e.g., requiring labeling changes) or major(e.g., 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, and 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. Drug approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

One of the performance goals agreed to by the FDA under the PDUFA is to complete its review of 90% of standard new molecular entity, or NME, NDAs within ten months from the filing date and 90% of priority NME NDAs within six months from the filing date, 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, within the last three months before the PDUFA goal date, the FDA requests (or the application sponsor otherwise provides) a substantial amount of new data or new information not previously submitted to, or reviewed by, the FDA (e.g., a major new clinical safety or efficacy study report, a proposed REMS), or a new analysis or major reanalysis of studies previously submitted to the pending application.

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 will be 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 or are otherwise inconsistent with 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. An 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.

Fast Track Designation, Priority Review, Breakthrough Therapy Designation and Accelerated Approval

The FDA has various programs, including fast track designation, priority review, breakthrough therapy designation and accelerated approval, which are intended to expedite or simplify the process for the development and FDA 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. While these pathways can reduce the time it takes for the FDA to review an NDA, they do not guarantee that a product will receive FDA approval.

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a drug is intended to treat a serious or life threatening disease or condition for which there is no effective treatment and demonstrates the potential to address an unmet medical need for the disease or condition. Under the fast track program, the sponsor of a drug candidate may request the FDA to designate the product for a specific indication as a fast track product concurrent with or after the filing of the IND for the drug candidate. The FDA must make a fast track designation determination within 60 days after receipt of the sponsor's request. In addition to other benefits, such as the ability to use surrogate endpoints and have greater interactions with the FDA, the FDA may initiate review of sections of a fast track product's NDA before the application is complete. This rolling review is available if the applicant provides, and the FDA approves, a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the NDA is submitted. A fast track drug also may be eligible for accelerated approval and priority review. In addition, the fast track designation may be withdrawn by the FDA if it believes that the designation is no longer supported by data emerging in the clinical trial process.

The FDA may give a priority review designation to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. These six- and ten-month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

Under the provisions of the new Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted by Congress in 2012, a sponsor can request designation of a drug candidate as a "breakthrough therapy," typically by the end of the drug's Phase II trials. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. For breakthrough therapies, the FDA may take certain actions, such as intensive and early guidance on the drug development program, that are intended to expedite the development and review of an application for approval.

FDASIA also codified and expanded on FDA's accelerated approval regulations, under which FDA may approve a drug for a serious or life threatening illness that provides meaningful therapeutic benefit over existing treatments based on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. A surrogate endpoint is a marker that does not itself measure clinical benefit but is believed to predict clinical benefit. This determination takes into account the severity, rarity or prevalence of the disease or condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform Phase IV or post marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for the FDA review or approval will not be shortened. Furthermore, fast track designation, priority review, accelerated approval and breakthrough therapy designation, do not change the standards for approval and may not ultimately expedite the development or approval process.

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. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug 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 rare pediatric disease, or 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 can be redeemed to receive a priority review of a subsequent marketing application for a different product. Such vouchers are transferable to another company.

If a product candidate 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 drug 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 same indication for which the orphan drug has exclusivity or obtain approval for the same product but for a different indication for which the orphan drug has exclusivity. Orphan drug exclusivity also could block the approval of one of our product candidates for seven years if a competitor obtains approval of the same product for the same orphan indication as defined by the FDA, or if our product candidate is determined to be contained within the competitor's product for the same orphan indication or disease. If a product candidate designated as an orphan drug receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan drug exclusivity. Orphan drug status in the EU has similar, but not identical, benefits, including up to ten years of exclusivity.

In *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021), the court disagreed with the FDA's longstanding position that the orphan drug exclusivity only applies to the approved use or indication within an eligible disease, and not to all uses or indications within the entire disease or condition. In particular, the circuit court held that the orphan drug exclusivity for Catalyst's drug blocked the FDA's approval of another drug for all uses or indications within the same orphan-designated disease, Lambert-Eaton myasthenic syndrome (LEMS), even though Catalyst's drug was approved at that time only for use in the treatment of LEMS in adults. Accordingly, the court ordered the FDA to set aside the approval of a drug indicated for LEMS in children. This decision created uncertainty in the application of orphan drug exclusivity. On January 24, 2023, the FDA published a notice in the Federal Register to clarify that while the agency complied with the court's order in Catalyst, the FDA intends to continue to apply its longstanding interpretation of the regulations to matters outside of the scope of the Catalyst order – that is, the agency will continue tying the scope of orphan drug exclusivity to the uses or indications for which a drug is approved, which permits other sponsors to obtain approval of a drug for new uses or indications within the same orphan-designated disease or condition that have not yet been approved. It is unclear how future litigation, legislation, agency decisions and administrative actions will impact the scope of orphan drug exclusivity.

Controlled Substance Regulation

The United States Controlled Substances Act, or CSA, establishes registration, security, recordkeeping, reporting, storage, distribution and other requirements administered by the Drug Enforcement Administration, or DEA. The DEA is concerned with the control of handlers of controlled substances, and with the equipment and raw materials used in their manufacture and packaging, in order to prevent loss and diversion into illicit channels of commerce. The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have a high potential for abuse, have no established medicinal use, and may not be marketed or sold in the U.S. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances. Annual registration is required for any facility that manufactures, distributes, dispenses, imports or exports any controlled substance. The registration is specific to the particular location, activity and controlled substance schedule. For example, separate registrations are needed for import and manufacturing, and each registration will specify which schedules of controlled substances are authorized.

The DEA typically inspects a facility to review its security measures prior to issuing a registration. Security requirements vary by controlled substance schedule, with the most stringent requirements applying to Schedule I and Schedule II substances. Required security measures include background checks on employees and physical control of inventory through measures such as cages, surveillance cameras and inventory reconciliations. Records must be maintained for the handling of all controlled substances, and periodic reports made to the DEA. Reports must also be made for thefts or losses of any controlled substance, and to obtain authorization to destroy any controlled substance. In addition, special authorization and notification requirements apply to imports and exports.

The DEA conducts periodic inspections of certain registered establishments that handle controlled substances. Failure to maintain compliance with applicable requirements, particularly as manifested in loss or diversion, can result in enforcement action that could have a material adverse effect on our business, results of operations and financial condition. The DEA may seek civil penalties, refuse to renew necessary registrations, or initiate proceedings to restrict, suspend or revoke those registrations. In certain circumstances, violations could result in criminal proceedings. Individual states also regulate controlled substances, and we and our contract manufacturers will be subject to state regulation on distribution of these products, including licensing, recordkeeping and security.

Controlled substances are also regulated pursuant to several international drug control treaties. These treaties are enforced by the United National Commission on Narcotic Drugs. The U.S. is a signatory to these treaties and thus must conform its laws and regulations to the international requirements, which generally include licensing, recordkeeping and reporting requirements. Any change in the international treaties regarding classification of these products could affect regulation of these substances in the U.S. and in other countries. Further, marketing approval and controlled substance classification procedures vary among countries, can involve additional testing and administrative review periods and may be otherwise complicated if our product candidates contain ingredients already classified as controlled substances in the countries where we develop them, which could make such product candidates subject to applicable controlled substances laws prior to commercialization. Foreign regulation of controlled substances can differ significantly from U.S. DEA and state regulations. The time required to obtain marketing approval and controlled substance classification in other countries may differ from and be longer than that required to obtain FDA approval and DEA classification in the U.S.

U.S. Patent Term Extension 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 Act. The Hatch-Waxman Act permits a patent term extension of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. Patent term extension 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 extension and the application for the patent term extension must be submitted within 60 days of receipt of FDA approval. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension.

Under the Hatch-Waxman Act, a drug product containing a new chemical entity as its active ingredient is entitled to five years of market exclusivity. A drug product is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is defined as the molecule or ion responsible for the activity of the drug substance, excluding those appended portions of the molecule that cause the drug to be an ester, salt, or other noncovalent derivative. During this exclusivity period, the FDA may not approve an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company that contains the previously approved active moiety. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

A drug product whose active ingredient was previously FDA-approved, and for which the sponsor is required to generate new clinical investigations such as to support new indications, dosages, strengths or dosage forms, is entitled to three years of market exclusivity. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original unmodified drug product, although the approval of such an application may not be effective until, at the earliest, after the full five years of market exclusivity has expired.

A drug product can also obtain pediatric market exclusivity in the U.S. and, if granted, adds six months to existing marketing exclusivities and any Orange Book-listed patent term(s). This six-month exclusivity, which runs from the end of other exclusivity periods and/or patent term(s), 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, even if the data do not show that the drug product was effective in the pediatric population studied.

Additional Regulation

Manufacturing, sales, promotion and other activities following drug approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the Drug Enforcement Administration for controlled substances, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments. In the United States, the activities of pharmaceutical manufacturers are subject to federal and state laws designed to prevent "fraud and abuse" in the healthcare industry. The laws generally limit financial interactions between manufacturers and health care providers or other participants in the healthcare industry and/or require disclosure to the government and public of such interactions. Many of these laws and regulations contain ambiguous requirements or require administrative guidance for implementation. Pharmaceutical manufacturers are also required to provide discounts or rebates under government healthcare programs or to certain government and private purchasers in order to obtain coverage under federal healthcare programs such as Medicaid. Participation in such programs may require tracking and reporting of certain drug prices. Manufacturers are subject to fines and other penalties if such prices are not reported accurately. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Drugs must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The failure to comply with regulatory requirements subjects manufacturers to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, recall or seizure of drugs, total or partial suspension of production, denial or withdrawal of product approvals, exclusion from participation in government healthcare programs or refusal to allow a firm to enter into supply contracts, including government contracts. In addition, even if a firm complies with FDA and other requirements, new information regarding the safety or efficacy of a product could lead the FDA to modify or withdraw product approval. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

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, controlled substances, 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 candidate, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product candidate 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.

The requirements and processes 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 Clinical Trials Regulation EU No 536/2014, or the CTR, which replaced the Clinical Trials Directive, entered into application on January 31, 2022, harmonizes the procedures for the submission, assessment and monitoring of clinical drug trials in the EU, thus simplifying the current rules for clinical trial authorization and standards of performance. The CTR requires a clinical trial sponsor to obtain approval from the national competent authority (NCA) of each European Union member state in which the clinical trial is to be conducted. Furthermore, the sponsor can only start a clinical trial at a specific study site after the local research ethics committee, or REC, has issued a favorable opinion. Subject to the transition arrangement referenced below, a sponsor submits a single application for a clinical trial authorization, or CTA, through a centralized EU clinical trials portal called the Clinical Trials Information System, or CTIS. One NCA (the reporting EU member state selected by the sponsor) takes the lead in validating and evaluating the application, as well as consulting and coordinating with the other concerned member states in which the clinical trial is to be conducted. If an application is rejected, it may be amended and resubmitted through CTIS. A concerned member state may in limited circumstances declare an "opt-out" from an approval and prevent the clinical trial from being conducted in that member state. The CTR foresees a three-year transition period. As of January 31, 2023, all new CTA applications had to be submitted via CTIS and be made pursuant to the CTR. From and after January 31, 2025, any trials approved under the Clinical Trial Directive (now replaced by the CTR) which are still ongoing will need to comply with the CTR and be recorded in CTIS.

In the UK, clinical trials of medicinal products for human use are primarily governed by the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). Similar to the EU, before a clinical trial can be initiated in the UK, a CTA must be obtained from the Medicines and Healthcare products Regulatory Agency, or MHRA, as well as a positive opinion from a REC.

To obtain regulatory approval of an investigational drug under EU regulatory systems, we must submit a marketing authorization application, or MAA. There are two types of marketing authorizations:

- The centralized MA is issued by the European Commission through the centralized procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or the CHMP, of the EMA, and is valid throughout the entire territory of the EEA. The centralized procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, advanced-therapy medicinal products (gene-therapy, somatic cell-therapy or tissue-engineered medicines) and medicinal products containing a new active substance indicated for the treatment of human immunodeficiency virus, acquired immunodeficiency syndrome, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases. The centralized procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU. Under the centralized procedure, the maximum timeframe for the evaluation of a MA application by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. Clock stops may extend the timeframe of evaluation of a MA application considerably beyond 210 days. Where the CHMP gives a positive opinion, the EMA provides the opinion together with supporting documentation to the European Commission, who makes the final decision to grant a MA, which is ordinarily issued within 67 days of receipt of the EMA's recommendation. Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of a MA application under the accelerated assessment procedure is 150 days, excluding clock stops, but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that the application is no longer appropriate to conduct an accelerated assessment.
- National MAs, which are issued by the NCAs of the EEA member states and only cover their respective territory, are available for products not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in a member state of the EEA, this national MA can be progressively recognized in other EEA member states through the mutual recognition procedure. If the product has not received a national MA in any EEA member state at the time of application, it can be approved simultaneously in various EEA member states through the decentralized procedure. Under the decentralized procedure, an identical dossier is submitted to the NCAs of each of the EEA member states in which the MA is sought, one of which is selected by the applicant as the Reference Member State (the RMS). The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics (SmPC), and a draft of the labeling and package leaflet, which are sent to the other EEA member states, referred to as the Concerned Member States, for their approval. If the Concerned Member States raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all EEA member states to which an application was submitted.

In relation to the UK, until the end of 2024, under the Northern Ireland Protocol which is contained in the Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, centralized MAs continue to provide a valid basis for commercializing medicinal products in Northern Ireland. However, centralized MAs no longer provide a valid basis for the commercialization of medicinal products in Great Britain. Pursuant to the Windsor Framework (which is a political declaration by the European Commission and the UK Government to correct the post-Brexit restrictions of movements of goods including medicines), from January 1, 2025, all new medicinal products for the UK market will be authorized by the MHRA which will grant on behalf of the UK Licensing Authority a single UK-wide MA for all medicinal products intended for sale in the UK, enabling medicinal products to be sold in a single pack and under a single authorization throughout the UK, including Northern Ireland, but the UK packaging must carry a clearly legible 'UK only' to be allowed onto the UK market.

Since leaving the EU, the MHRA has introduced changes to national licensing procedures, including procedures to prioritize access to new medicines that will benefit patients, an accelerated assessment procedure, and new routes of evaluation for novel products and biotechnological products. There is no wholesale recognition of EU pharmaceutical legislation between the jurisdictions, and EU MAs do not automatically provide a valid basis for the commercialization of medicinal products in Great Britain, From January 1, 2024, companies are able to request the MHRA to recognize MAs granted by acceptable Reference Regulators in foreign jurisdictions (including the EU) under a new International Recognition Procedure, or IRP. IRP allows the MHRA to take into account the expertise and decision-making of trusted regulatory authorities to conduct targeted assessments of IRP applications while retaining the authority to reject applications if the evidence provided is considered insufficiently robust.

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 data and market exclusivity. For example, in the EU, upon receiving marketing authorization, innovative medicinal products (including both small molecules and biological medicinal products) approved on the basis of a complete independent data package consisting of quality, preclinical testing results, and clinical trial data receive eight years of data exclusivity upon grant of an MA, and an additional two years of marketing exclusivity. If granted, data exclusivity prevents generic or biosimilar applicants from cross-referencing the innovator's preclinical and clinical trial data contained in the dossier of the reference medicinal product when applying for a generic or biosimilar MA until the data exclusivity period has expired. Even if a generic and a biosimilar product is approved, it can be marketed only until the expiration of the full ten-year exclusivity period. The overall ten-year period can be extended to a maximum of 11 years if, during the first eight years of those ten years, the MA holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are determined to bring a significant clinical benefit in comparison with currently approved therapies. The UK domestic law follows the same formula of regulatory data and marketing exclusivity. However, there is no guarantee that a product will be considered by the EU's regulatory authorities to be a new chemical entity or new active substance, and products may not qualify for data exclusivity.

Products receiving orphan designation in the EU can receive ten years of market exclusivity, provided that the orphan designation is maintained at the time of grant of the marketing authorization. During the ten-year orphan market exclusivity period, no application for a similar medicinal product for the same indication may be accepted by any regulatory authority in the EU for approval. An orphan product can also obtain an additional two years of market exclusivity in the EU for completing pediatric studies in compliance with an agreed Pediatric Investigation Plan even though the data do not lead to approval of a pediatric indication. 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 but not identical 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. The criteria for orphan designation must be re-assessed and confirmed at the time when a marketing authorization is granted in order to benefit from a period of 10 years orphan market exclusivity. The MHRA conducts an equivalent assessment, against the criteria specific to the UK. In the EEA, orphan drug designation must be requested before submitting an application for MA. The EMA's Committee for Orphan Medicinal Products (COMP) is required to re-assess the granted orphan designation at the time of MA grant to ensure that it continues to meet the criteria for the designation to be maintained. Otherwise, the orphan designation can be revoked. In contrast, the MHRA does not grant orphan designations during the development of the medicinal product. Instead, the MHRA will decide whether the criteria are satisfied at the point of grant of an MA.

In the EEA and the UK, 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 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 medicinal product for the same therapeutic 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.

A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication.

In the EEA, companies developing a new medicinal product must agree upon a pediatric investigation plan ("PIP"), with the EMA's Pediatric Committee (the "PDCO"), and must conduct pediatric clinical trials in accordance with that PIP, unless a waiver applies. The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when this data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Products that are granted a MA with the results of the pediatric clinical trials conducted in accordance with the PIP (even where such results are negative) are eligible for six months' supplementary protection certificate extension (if any is in effect at the time of approval). In the case of orphan medicinal products, a two-year extension of the orphan market exclusivity may be available. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted. According to local law requirements, the UK MHRA adopts a similar approach to the EEA to facilitate the development of medicinal products for the pediatric population.

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, and private payers such as private health insurance and managed care plans, and other organizations. These third-party payers may deny or limit coverage or reimbursement for a product.

Within the U.S., coverage and reimbursement for drug products can differ significantly from payer to payer. One third-party payer's decision to cover a particular drug product or service does not ensure that other payers will also provide coverage for the product or will provide coverage at an adequate reimbursement rate. Third-party payers may attempt to control costs by limiting coverage (e.g., 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), by controlling utilization (e.g., requiring pre-approval or prior authorization for new or innovative drug therapies before they will provide coverage for specific patients) and by limiting the amount of reimbursement for drugs.

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.

While we cannot predict what cost-containment measures will be adopted or otherwise implemented in the future, new measures or any announcement of proposed measures 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 U.S. 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 generally and drug costs specifically.

In the U.S., for example, the Patient Protection and Affordable Care Act, as amended, or PPACA, is a sweeping law enacted in March of 2010 that expanded health care coverage through Medicaid expansion and the implementation of the individual mandate for health insurance coverage and which included changes to the coverage and reimbursement of drug products under government healthcare programs. Beyond the PPACA, there are ongoing and widespread health care reform efforts, a number of which have focused on regulation of prices or payment for drug products. Drug pricing and payment reform was a focus of the Trump Administration and has been a focus of the Biden Administration. For example, federal legislation enacted in 2021 eliminates a statutory cap on Medicaid drug rebate program rebates effective January 1, 2024. As another example, the Inflation Reduction Act (IRA) of 2022 contains various drug price negotiation, inflationary rebate, and pricing provisions with varying implementation dates.

The IRA allows the federal government to negotiate a maximum fair price for certain high-priced single-source Medicare drugs, imposes penalties and excise tax for manufacturers that fail to comply with the drug price negotiation requirements, requires inflation rebates for all Medicare Part B and Part D drugs (with limited exceptions) if their drug prices increase faster than inflation, and redesigns Medicare Part D to reduce out-of-pocket prescription drug costs for beneficiaries, among other changes. The impact of the IRA on our business and the broader pharmaceutical industry remains uncertain as implementation is ongoing. As another example, in 2022, subsequent to the enactment of the IRA, the Biden administration released an executive order directing the HHS to report on how the Center for Medicare and Medicaid Innovation ("CMMI") could be leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. The report was issued in 2023 and proposed various models that CMMI is currently developing which seek to lower the cost of drugs, promote accessibility and improve quality of care. These changes or other changes could affect the market conditions for our products. We expect continued scrutiny on drug pricing and government price reporting from Congress, agencies, and other bodies.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. For example, on January 5, 2024, the FDA approved Florida's Section 804 Importation Program, or SIP, proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs. Additionally, a number of states have enacted state drug price transparency and reporting laws that could substantially increase our compliance burdens and expose us to greater liability under such state laws if and when we have marketed products.

Healthcare reform efforts have been and may continue to be subject to scrutiny and legal challenge. For example, with respect to the PPACA, tax reform legislation was enacted that eliminated the tax penalty established for individuals who do not maintain mandated health insurance coverage beginning in 2019 and, in 2021, the U.S. Supreme Court dismissed the latest judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the PPACA. As another example, revisions to regulations under the federal anti-kickback statute would remove protection for traditional Medicare Part D discounts offered by pharmaceutical manufacturers to pharmacy benefit managers and health plans. Pursuant to court order, the removal was delayed and recent legislation imposed a moratorium on implementation of the rule until January 2032. As another example, the IRA drug price negotiation program has been challenged in litigation filed by various pharmaceutical manufacturers and industry groups.

We expect that healthcare reform measures that have been or in the future may be adopted, 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 any future revenue generation. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payers. Complying with any new legislation and regulatory changes could be time-intensive and expensive, resulting in a material adverse effect on our business.

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

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 a condition of obtaining reimbursement or pricing approval, the completion of clinical trials that compare the cost-effectiveness of a particular product to other then-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.

On May 1, 2021, the EU and UK trade and cooperation agreement, or TCA, entered into application. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of the outcomes of GMP inspections. Applicants and MA holders may submit GMP certificates issued by the MHRA for sites located outside the EU/EEA as supporting information for EU regulatory submissions. However, the TCA does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. The regulatory regime in Great Britain currently broadly aligns with EU regulations. However, it is possible that these regimes may diverge in the future, given proposed legislative changes such as the European Commission's proposals for the entire overhaul of the pharmaceutical regulatory regime.

Other Healthcare Laws and Compliance Requirements

In the United States, pharmaceutical manufacturers are subject to numerous other federal, state and local laws designed to, for example, prevent fraud and abuse; promote transparency in interactions with others in the healthcare industry; regulate pricing of drugs and protect the privacy of individual information. These laws are enforced by various federal and state enforcement authorities, including but not limited to, the U.S. Department of Justice, and individual U.S. Attorney offices within the Department of Justice, the U.S. Department of Health and Human Services, or HHS, HHS' various divisions, including but not limited to, the Centers for Medicare & Medicaid Services, or CMS, and the Office of Inspector General, and state boards of pharmacy.

We may be subject to various federal and state laws pertaining to health care "fraud and abuse," including anti kickback laws, and false claims laws, for activities related to past and future sales of any products reimbursable by third party payers such as federal health care programs (including Medicare and Medicaid) or, in some cases, commercial health plans. Anti-kickback laws generally prohibit a pharmaceutical manufacturer from soliciting, offering, receiving, or paying anything of value to generate business, including the purchase, prescription or use of a particular drug. False claims laws generally prohibit anyone from knowingly and willingly presenting, or causing to be presented, any claims for payment for reimbursed drugs or services to third-party payers that are false or fraudulent. Although the specific provisions of these laws vary, their scope is generally broad and there may not be regulations, guidance or court decisions that apply the laws to particular industry practices. There is therefore a possibility that our practices might be challenged under such laws.

Laws and regulations have also been enacted by the federal government and various states to regulate the sales and marketing practices of pharmaceutical manufacturers with marketed products. The laws and regulations generally limit financial interactions between manufacturers and health care providers; require manufacturers to adopt certain compliance standards; require disclosure to the government and public of financial interactions; require disclosure of marketing expenditures or pricing information, regulate drug pricing and/or require the registration of pharmaceutical sales representatives. Many of these laws and regulations contain ambiguous requirements or require administrative guidance for implementation. Given the lack of clarity in laws and their implementation, any future activities (if we obtain approval and/or reimbursement from federal healthcare programs for our product candidates) could be subject to challenge.

Federal laws, including the Medicaid Drug Rebate Program, require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under government healthcare programs. These laws are complex and the failure to calculate reported prices correctly or provide appropriate prices and rebates can expose a manufacturer to penalties and other sanctions.

The distribution of drugs and biological products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

Federal and state consumer protection and unfair competition laws and regulations broadly regulate marketplace activities and that potentially harm consumers and could apply to the activities of pharmaceutical manufacturers.

We may be subject to data privacy and security laws in the various jurisdictions in which we operate, obtain or store personally identifiable information. Numerous U.S. federal and state laws govern the collection, use, disclosure and storage of personal information. Various foreign countries also have, or are developing, laws governing the collection, use, disclosure and storage of personal information. Globally, there has been an increasing focus on privacy and data protection issues that may affect our business.

Efforts to ensure that our activities comply with applicable healthcare laws and regulations will involve substantial costs. Given the breadth of the laws and regulations, limited guidance for certain laws and regulations and evolving government interpretations of the laws and regulations, governmental authorities may possibly conclude that our business practices may not comply with such laws. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. Further, defending against any such actions can be costly, time-consuming and may require significant personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

To the extent that any of our products are sold in a foreign country or if we contract with vendors or independent contractors outside of the U.S., we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-approval requirements, including safety surveillance, anti-corruption/anti-bribery laws, anti-kickback laws, healthcare fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals. While we are not aware of any current issues, we are unable to predict whether we will be subject to actions under applicable healthcare laws, or the impact of such actions on our business. However, the costs of defending such actions or claims, as well as any sanctions imposed, could result in a material adverse effect on our business or financial condition.

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 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 laws or development of new regulations will affect our business operations or the cost of compliance.

Human Capital

Our board of directors and management recognize that creating long-term enterprise value is advanced by considering the interests and concerns of many stakeholders, including those of our employees. As of December 31, 2023, we had 259 employees, including 251 full-time and part-time permanent employees, of which 179 are located in Canada and 72 are located in the U.S. Of our employees, 190 were primarily engaged in research and development, 78 of whom hold a Ph.D. or M.D. (or equivalent) degree, and 69 were engaged in general and administrative or commercial activities. 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.

As competition for qualified personnel in the biotechnology and pharmaceutical field is intense, attracting and retaining qualified employees at all levels is critical to our business. We continuously strive to ensure that employee morale remains strong, and conduct employee engagement surveys to identify areas of focus and monitor employee turnover rates. As of December 31, 2023, and for the last several years, our company turnover rate was and has been lower than the industry market average.

We have established comprehensive and competitive compensation and benefits programs to attract and retain highly qualified personnel and to incentivize and reward strong performance. In addition to providing our employees with competitive salaries, we believe that employees should share in the potential financial gains resulting from the advancement of our programs by way of annual bonuses to permanent employees based on the achievement of corporate and/or personal objectives. To align the interests of our employees with those of our shareholders, we award stock options to all permanent employees, both upon initial hiring and annually thereafter. Our leave programs include paid vacation, personal, sick, disability and other paid and unpaid leaves. Our health and wellness programs include medical, dental, vision care, retirement savings, employee assistance programs, flexible work schedules and other benefits.

As a biopharmaceutical company with highly educated employees, we believe that our employees must stay current with advances in our industry and continue to grow in their careers. We support our employees' further development through a variety of internal training and external professional development opportunities, including conference attendance and tuition reimbursement.

We are committed to diversity, equity, inclusion and accessibility, or DEIA, at all levels of our company, and we have established a joint management/employee committee to progress these important issues. We will continue to focus on measuring and extending our diversity and inclusion initiatives across our entire workforce. We recruit the best-qualified employees regardless of sex, gender, ethnicity, race, religion, or other protected traits, and it is our policy to comply with all applicable laws related to discrimination in the workplace.

Manufacturing

We currently rely, and expect to continue to rely, on third-party contract manufacturers, or CMOs, to manufacture (or produce sufficient quantities of materials required for the manufacture of) our product candidates for pre-clinical testing and clinical trials, and we intend to do so for the commercial manufacture of our products. Similarly, we may rely on collaborators to manufacture, either directly or through CMOs, product candidates licensed to them. 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 and suppliers. 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, excipients and packaging components.

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 had one wholly-owned subsidiary as of December 31, 2023, Xenon Pharmaceuticals USA Inc., which was incorporated in Delaware on December 2, 2016. Our principal executive offices are located at 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., 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. 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. Our Risk Factors are not guarantees that no such conditions exist as of the date of this report and should not be interpreted as an affirmative statement that such risks or conditions have not materialized, in whole or in part.

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.

Investment in biopharmaceutical product development is highly speculative because it entails substantial capital expenditures and significant risk that a product candidate may fail to demonstrate adequate efficacy or an acceptable safety profile, gain regulatory approval and become commercially viable. We have no products approved for commercial sale and have not generated any revenue from product sales to date, and we will continue to incur significant research and development and other expenses related to our clinical development and ongoing operations. As a result, we are not profitable and have incurred losses in each period since our inception. Since our inception, we have devoted substantially all of our financial resources and efforts to research and development, including pre-clinical studies, manufacturing of investigational drug and our clinical trials. Our financial condition and operating results, including net losses, may fluctuate significantly from quarter to quarter and year to year. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance. We do not expect to have sustained profitability for the foreseeable future. We had net losses of $182.4 million, $125.4 million and $78.9 million for the years ended December 31, 2023, 2022 and 2021, respectively, and an accumulated deficit of $665.1 million as of December 31, 2023, 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 expect to continue to incur significant losses for the foreseeable future, and we expect these losses to increase as we continue our research and development of, and seek regulatory approvals for our product candidates.

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;
- conduct additional pre-clinical, clinical or other studies for our product candidates;
- manufacture, label, serialize and distribute drug substance and drug product for clinical trials and commercialization;
- seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical trials;
- hire and retain additional personnel, such as clinical, quality assurance, regulatory, scientific, commercial and administrative personnel;
- 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 1st Order Pharmaceuticals, Inc. and other third parties;
- maintain, protect and expand our intellectual property portfolio;
- establish sales, marketing, distribution and other commercial infrastructure to commercialize any products for which we may obtain marketing approval;
- create additional infrastructure and incur additional costs to support our operations and our product development and planned future commercialization efforts; and
- experience any delays or encounter adverse issues with respect to any of the above.

Our expenses could increase beyond expectations for a variety of reasons, including if we are required by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, or other regulatory authorities to perform clinical and other studies including post-approval commitments in addition to those that we currently anticipate, or if there are any delays in establishing appropriate manufacturing arrangements to support our clinical trials, the development of any of our product candidates or commercialization. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our shareholders' equity and working capital.

We do not generate any revenue from product sales and may never become profitable.

Our ability to generate revenue and achieve profitability depends on our ability, alone or with collaborators, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our product candidates. Successful commercialization will require achievement of many key milestones, including demonstrating safety and efficacy in clinical trials, obtaining regulatory, including marketing, approval for these product candidates, manufacturing, marketing and selling those products for which we, or any of our existing or future collaborators, may obtain regulatory approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payers. Because of the uncertainties and risks associated with these activities, we are unable to accurately and precisely predict the timing and amount of revenues, the extent of any further losses or if or when we might achieve profitability. We and our existing or future collaborators may never succeed in these activities and, even if we do, we may never generate revenues that are large enough for us to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Additionally, our expenses could increase if we are required by the FDA, EMA or other regulatory authorities to perform clinical trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates.

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. If we are unable to generate 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.

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

Since our inception, we have dedicated most of our resources to the discovery and development of our pre-clinical and clinical product candidates. We expect to continue to spend substantial amounts of resources to continue the pre-clinical and clinical development of our current and future programs. If we are able to gain marketing approval for product candidates that we develop, we will require significant additional amounts of capital in order to launch and commercialize such product candidates to the extent that such launch and commercialization are not the responsibility of a collaborator. In addition, other unanticipated costs may arise in the course of our development efforts. Because the design and outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of any product candidate we develop.

Our future capital requirements depend on many factors, including but not limited to:

- the scope, progress, results and costs of researching and developing our current product candidates, as well as additional product candidates we may develop and pursue in the future;
- the timing of, and the costs involved in, obtaining marketing approvals for our product candidates and any additional product candidates we may develop and pursue in the future;
- the number of future product candidates that we may pursue and their development requirements;
- if approved, the costs of commercialization activities for any product candidate that receives regulatory approval to the extent such costs are not the responsibility of an existing or future collaborator, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to the receipt of regulatory approval, revenue, if any, received from commercial sales of our product candidates and any additional product candidates we may develop and pursue in the future;
- whether our existing collaborations generate substantial milestone payments and, ultimately, royalties on future approved products for us;
- our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such arrangements;
- the costs associated with any transactions to acquire or in-license other product candidates and technologies;
- our headcount growth and associated costs as we expand our research and development efforts and initiate pre-commercial activities;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patents, including litigation costs and the outcome of such litigation; and

- the ongoing costs of operating as a public company.

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. 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. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, reduce or terminate our product development programs or plans for commercialization.

We may allocate our limited resources to pursue a particular product candidate or indication and fail to capitalize on other product 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 product candidates. As a result, we may forgo or delay pursuit of opportunities with other product candidates or for our current product candidates in 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 product 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 product candidate, we may relinquish valuable rights to that product 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.

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.

We expect our expenses to increase in connection with our planned operations. Unless and until we can generate a substantial amount of revenue from any approved product candidates, we expect to finance our future cash needs through public or private equity offerings, debt financings, royalty-based financing, collaborations, licensing arrangements or other sources, or any combination of the foregoing. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

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.

Historically, we have also financed our operations through the incurrence of debt. Any future incurrence of indebtedness would result in increased fixed payment obligations and, potentially, the imposition of restrictive covenants. Such 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 collaborations or marketing, distribution or licensing arrangements, or royalty-based financings with third parties, and we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional capital when needed, we may be required to delay, reduce or terminate our product discovery and development programs, commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves. 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.

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

As of December 31, 2023, approximately 3% 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 and Industry

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 drug 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 and/or tolerability, convenience and ease of administration, price, the potential advantages 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 or other foreign 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.

If one or more of our proprietary or partnered products were approved for the treatment of epilepsy, we anticipate that they could potentially compete with other anti-seizure medications, or ASMs, or one another. In addition, if one or more of our proprietary products were approved for the treatment of major depressive disorder, or MDD, we anticipate that they could potentially compete with other anti-depressant medications, or ADs.

We have no marketed proprietary products and have not yet completed clinical development 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 previous experience in completing a Phase 3 clinical trial and related regulatory requirements including a New Drug Application, or NDA, or equivalent submission, or the commercialization of products. We have not yet demonstrated our ability to independently and repeatedly conduct clinical development after Phase 2, obtain regulatory approval, manufacture drug substance or drug product on a registrational and 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. To execute on our business plan for the development of independent programs, we will need to successfully:

- reach agreement with multiple regulatory agencies on clinical and pre-clinical studies required for registration;
- execute our clinical development and manufacturing 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 pre-commercialization capabilities as well as commercial sales, distribution and marketing capabilities;
- build and implement effective market access strategy and 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, developing and commercializing additional product candidates, 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 through acquiring or in-licensing other product candidates or technologies. 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 through 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.

If we fail to attract and retain our executive officers 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. Our industry has experienced a high rate of turnover of management personnel in recent years. Replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully.

We are highly dependent upon our executive officers, including Mr. Ian Mortimer, our President and Chief Executive Officer. The loss of services of one or more of our executive officers 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 legal and regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of fraud or other misconduct by our employees, collaborators, vendors, investigational site staff, consultants, commercial partners and other personnel. Misconduct by those parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates:

- the regulations of the FDA, EMA and other foreign regulators, including those laws requiring the reporting of true, complete and accurate information to such authorities;
- manufacturing standards;
- insider trading laws;
- data privacy, data protection and security;
- federal and state healthcare fraud and abuse laws and regulations in the U.S. and abroad; and
- laws that require the reporting of financial information or data accurately.

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, we are subject to applicable foreign, federal and state data privacy and security laws. For additional information, see "Risk Factors — We are subject to evolving global laws and regulations relating to privacy, data protection and information security, which may require us to incur substantial compliance costs, and any failure or perceived failure by us to comply with such laws and regulations may harm our business and operations."

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 or misrepresentation of information obtained in the course of clinical trials or creating fraudulent data in our pre-clinical studies or clinical trials, 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 claims, demands, or lawsuits stemming from an actual or alleged failure to comply with these laws and regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves, achieving a favorable settlement or otherwise asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, disgorgement, integrity oversight and reporting obligations, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations. Additionally, defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

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. In order to execute on this strategy, we will need to build out a regulatory, sales, manufacturing, supply chain 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, compensate our employees on adequate terms in an increasingly competitive, inflationary market and continue to implement and improve our managerial, operational and financial systems. As our operations expand, we expect that we will need to manage additional relationships with various strategic collaborators, suppliers and other third parties.

Future growth will impose significant added responsibilities on members of management including the need to identify, recruit, maintain, motivate and integrate additional employees. Also, 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. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our business, give rise to operational errors, loss of business opportunities, loss of employees and reduced productivity amongst remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of existing and additional product candidates. 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.

We are subject to evolving global laws and regulations relating to privacy, data protection and information security, which may require us to incur substantial compliance costs, and any failure or perceived failure by us to comply with such laws and regulations may harm our business and operations.

In the ordinary course of business, we process personal data and other sensitive information, including our proprietary and confidential business data, trade secrets, intellectual property, data about trial participants collected in connection with clinical trials, and other sensitive data. Our data processing activities subject us to numerous data privacy and security obligations, such as various laws, regulations, guidance, industry standards, external and internal privacy and security policies, contracts, and other obligations that govern the processing of personal data by us and on our behalf.

In the U.S., federal, state, and local governments have enacted numerous data privacy and security laws, including data breach notification laws, personal data privacy laws, and consumer protection laws. For example, the U.S. 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, imposes specific requirements relating to the privacy, security, and transmission of individually identifiable health information that apply to most U.S. health care providers with which we interact, such as our U.S. clinical trial sites. At the state level, the California Consumer Privacy Act of 2018, or CCPA, as amended and supplemented by the California Privacy Rights Act, imposes obligations on businesses to which it applies. The CCPA allows for statutory fines for noncompliance. Although the CCPA exempts some data processed in the context of clinical trials, the CCPA, to the extent applicable to our business and operations, may increase compliance costs and potential liability with respect to other personal information we maintain about California residents. Other states have also enacted data privacy laws. Additional data privacy and security laws have been proposed at the federal, state, and local levels in recent years, which could further complicate compliance efforts.

Outside the U.S., the European Union's General Data Protection Regulation, or EU GDPR, and the United Kingdom's GDPR, or UK GDPR, impose strict requirements for processing the personal data of individuals. For example, under the EU GDPR, government regulators may impose temporary or definitive bans on data processing, as well as fines of up to 20 million euros or 4% of annual global revenue, whichever is greater. Further, individuals may initiate litigation related to our processing of their personal data. Certain foreign jurisdictions have enacted data localization laws and cross-border personal data transfer laws, which could make it more difficult to transfer information across jurisdictions, such as transferring or receiving personal data that originates in the European Union, or EU. Additional jurisdictions continue to enact and modify their data privacy laws, which increases the complexity of the data privacy landscape.

Although we endeavor to comply with all applicable data privacy and security obligations, these obligations are quickly changing in an increasingly stringent fashion, creating some uncertainty as to how to comply, and potentially requiring us to modify our policies and practices, which may be costly and may divert the attention of management and technical personnel. Further, we may at times fail, or be perceived to have failed, to have complied and could face significant consequences. These consequences may include, but are not limited to, government enforcement actions, investigations and other proceedings; additional reporting requirements and/or oversight; bans on processing personal data; orders to destroy or not use personal data; and imprisonment of company officials. Any of these events could have a material adverse effect on our reputation, business, or financial condition, including but not limited to: interruptions or stoppages in our business operations, including our clinical trials; inability to process personal data or to operate in certain jurisdictions; limited ability to develop or commercialize our products; expenditure of time and resources to defend any claim or inquiry; adverse publicity; or revision or restructuring of our operations.

Our business and operations could suffer in the event of an actual or perceived information security incident such as a cybersecurity breach, system failure, or other compromise of our systems and/or information, including information held by a third-party contractor or vendor.

We rely on both internal information technology systems and networks, and those of third-party vendors and contractors, to acquire, transmit, store and otherwise process information in connection with our business activities. Our ability to effectively manage our business depends on the security, reliability and adequacy of our and our third-party contractors' and vendors' technology systems. Any incident, whether hostile or inadvertent, that adversely impacts the confidentiality, integrity or availability of our systems and/or data, including phishing, business email compromise, social engineering, ransomware or other malware, or any security breach, security incident or other destruction, loss, or unauthorized use or other processing of data maintained or otherwise processed by us or on our behalf could result in a loss of intellectual property or misappropriation of trade secrets, disruptions to our business and operations, subject us to increased costs and require us to expend time and resources to address the matter, may subject us to claims, demands, and proceedings by private parties, regulatory investigations and other proceedings, and fines, penalties, and other liability and have a material adverse effect on our business. In addition, the loss, alteration or other damage to or other unavailability of pre-clinical data or clinical trial data from completed or ongoing clinical trials for our product candidates could result in delays in our development and regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Any cyber-attack, security breach or incident, or other destruction, loss or unauthorized processing of data maintained or otherwise processed by us or on our behalf, or the perception any such matter has occurred, could result in actual or alleged violations of applicable U.S. and international privacy, data protection, information security and other laws and regulations, harm our reputation and subject us to litigation and governmental investigations and proceedings by federal, state and local regulatory entities in the U.S. and by international regulatory entities, resulting in exposure to material civil and/or criminal proceedings and liability. In addition, we may incur significant additional expense to implement further measures relating to privacy, data protection and information security, whether in response to an actual or perceived security breach or incident or otherwise.

To date, we have not experienced any material impact to our business, financial position or operations resulting from cyberattacks or other information security incidents; however, because of frequently changing attack techniques, along with the increased volume and sophistication of such attacks, our business, financial position or operations could be adversely impacted in the future. Moreover, the increasingly distributed nature of computing, including prevalent use of mobile devices to access confidential information and widespread use of cloud-based applications hosted in remote data centers, increases the risk of security breaches and incidents. These risks may be heightened due to the increasing number of our and our third-party vendors' and contractors' personnel working remotely. As cyber threats continue to evolve, we may be required to expend significant additional resources to continue to modify or enhance our protective measures or to investigate and remediate information security vulnerabilities, threats and incidents. While we have implemented layered security measures, our computer systems and the external systems and services used by our third-party contract manufacturers, or CMOs, and contract research organizations, or CROs, and their vendors and contractors remain potentially vulnerable to these events and there can be no assurance that we will be successful in preventing cyber-attacks or successfully mitigating their effects. Our liability insurance may not be sufficient in type or amount to cover us against claims related to security breaches, cyberattacks and other related breaches.

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

We must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we operate and plan to operate outside the U.S., including those countries outside the U.S. in which we are conducting clinical trials. As we engage in significant cross-border and international activities, we will be subject to risks related to international operations, including:

- different regulatory requirements for conducting clinical trials, registering and maintaining approval of, manufacturing and advertising 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 payer reimbursement regimes, government payers 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;
- 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, the likelihood of which may increase with an increase of operations in foreign jurisdictions, directly or indirectly through third parties (whose corrupt or other illegal conduct may subject us to liability), which may involve interactions with government agencies or government-affiliated hospitals, universities and other organizations, such as conducting clinical trials, selling our products, and obtaining necessary permits, licenses, patent registrations, and other regulatory approvals;
- tighter restrictions on privacy and data protection, and more burdensome obligations associated with the collection, use and retention of data, including clinical data and genetic material, may apply in jurisdictions outside of North America;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- business interruptions resulting from geopolitical actions, including war, civil and political unrest and terrorism, or natural disasters including earthquakes, typhoons, floods and fires; and
- supply and other disruptions resulting from the impact of public health pandemics or epidemics on our strategic partners, third-party manufacturers, suppliers and other third parties upon which we rely.

If we are unable to successfully manage these risks associated with cross-border and international activities, 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 percentage of our assets (as determined under applicable Treasury Regulations, 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 our gross income and gross assets, we are deemed a PFIC for the taxable year ending December 31, 2023 and may be a PFIC for subsequent taxable 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 current taxable year or 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 pro rata shares of ordinary earnings and net capital gains for each year we believe we were 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, if we are or become a PFIC (or our PFIC status is uncertain), it 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.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

We have significant Canadian federal net operating loss carryforwards which are limited in life, Canadian federal investment tax credit carryforwards and provincial investment tax credit carryforwards which could expire unused and be unavailable to offset future income tax liabilities. The rules dealing with Canadian and U.S. federal, provincial, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Canada Revenue Agency, Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws, or changes in interpretations of existing laws (which changes may have retroactive application), including with respect to net operating losses and tax credits, could adversely affect us or holders of our common shares. In recent years, many such changes have been made and changes are likely to continue to occur in the future. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

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 income tax in jurisdictions outside of Canada and the U.S., if under the laws of any such jurisdiction, we are considered to be carrying on a trade or business there or earn income that is considered to be sourced there and we do not qualify for an exemption. In jurisdictions where we do not believe we are subject to tax, we can provide no certainty that tax authorities in those jurisdictions will not subject one or more tax years to examination. Tax examinations are often complex as tax authorities may disagree with the treatment of items reported by us, the result of which could have a material adverse effect on our operating results and financial condition.

Acquisitions or other strategic transactions could disrupt our business, cause dilution to our shareholders and otherwise harm our business.

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

- disruption in our relationships with collaborators or suppliers as a result of such a transaction;
- unanticipated liabilities related to acquired companies;
- difficulties integrating acquired personnel, technologies and operations into our existing business;
- retention of key employees;
- diversion of management time and focus from operating our business to pursuing strategic transactions and managing any such strategic alliances, joint ventures or acquisition integration challenges;
- dilution to our shareholders if we issue equity in connection with such transactions;
- increases in our expenses and reductions in our cash available for operations and other uses; and

- possible write-offs or impairment charges relating to acquired businesses.

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

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

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

Healthcare providers and third-party payers in the U.S. and elsewhere play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our arrangements with healthcare providers, third-party payers, patients and other parties within the healthcare industry may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell, and distribute any products for which we obtain marketing approval. Restrictions under applicable healthcare and data privacy laws and regulations include the following, some of which will apply only if and when we have a marketed product:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;
- federal civil and criminal false claims laws, including the federal False Claims Act, which can be enforced through civil whistleblower, or qui tam actions, as well as civil monetary penalty laws can impose criminal and civil penalties, assessment, and exclusion from participation for various forms of fraud and abuse involving the federal healthcare programs, such as Medicare and Medicaid;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended, which imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also establishes requirements related to the privacy, security, and transmission of individually identifiable health information which apply to many healthcare providers, physicians, and third-party payers with whom we interact;
- the FDCA, which, among other things, strictly regulates drug product and medical device marketing, prohibits manufacturers from marketing such products for off-label use and regulates the distribution of samples;
- federal laws that require pharmaceutical manufacturers to report certain calculated product prices to the government or provide certain discounts or rebates to government authorities or private entities, often as a condition of reimbursement under governmental healthcare programs;
- the so-called federal "sunshine law" or Open Payments which requires manufacturers of drugs, devices, biologics, and medical supplies to report to the Centers for Medicare & Medicaid Services information related to payments and other transfers of value to teaching hospitals, physicians, and other healthcare practitioners, as well as ownership and investment interests held by physicians and their immediate family members;
- federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payers, including private insurers; state and foreign laws that limit financial interactions between manufacturers and health care providers; require manufacturers to adopt certain compliance standards; require disclosure to the government and public of financial interactions; require disclosure of marketing expenditures or pricing information, regulate drug pricing and/or require the registration of pharmaceutical sales representatives;; and state and foreign laws governing the collection, export, privacy, use, protection and security of biological materials and health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Efforts to ensure that our activities comply with applicable healthcare laws and regulations will involve substantial costs. Given the breadth of the laws and regulations, limited guidance for certain laws and regulations and evolving government interpretations of the laws and regulations, governmental authorities may possibly conclude that our business practices may not comply with such laws. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. Further, defending against any such actions can be costly, time-consuming and may require significant personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

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

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

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

Our headquarters are located in Burnaby, British Columbia, Canada. We are vulnerable to natural disasters such as earthquakes that could disrupt our operations. If a natural disaster, power outage, fire or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our CMOs, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. Although we carry insurance for earthquakes and other natural disasters, we may not carry sufficient business interruption insurance to compensate us for all losses that may occur. The disaster recovery and business continuity plans we have in place may not be adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of a natural disaster or earthquake, which could have a material adverse effect on our business. In addition, we may lose samples or other valuable data. The occurrence of any of the foregoing could have a material adverse effect on our business.

Risks Related to the Discovery, Development and Commercialization of Our Product Candidates

Our business substantially depends upon the successful development of XEN1101. If we are unable to obtain regulatory approval for, and successfully commercialize, XEN1101, our business may be materially harmed.

We currently have no products approved for commercial sale and are investing significant efforts and financial resources in the development of our clinical-stage product candidate, XEN1101 for the treatment of epilepsy, MDD and potentially other neurological disorders. Our future business success depends on the continued development and ultimate regulatory approval of XEN1101. We will need to successfully enroll and complete our XEN1101 Phase 3 epilepsy clinical trials and any other future Phase 3 clinical trials. The future regulatory and commercial success of XEN1101 is subject to a number of risks, including:

- successful patient enrollment in clinical trials and ultimate completion of clinical trials;
- successful efficacy data from our clinical programs that support acceptable risk-benefit profiles of XEN1101 in the intended patient populations;
- receipt and maintenance of marketing approvals from applicable regulatory authorities;
- completing any post-marketing studies required by applicable regulatory authorities;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for XEN1101;
- making arrangements with third-party manufacturers for both clinical and commercial supplies of XEN1101;

- establishing sales, marketing and distribution capabilities and commercial launch of XEN1101, if and when approved, whether alone or in collaboration with others;
- successful commercial launch of XEN1101, if and when approved;
- acceptance of XEN1101, if and when approved, by patients, the medical community and third-party payers;
- obtaining and maintaining acceptable pricing, third-party insurance coverage and adequate reimbursement;
- maintaining a continued acceptable safety profile of XEN1101 following approval;
- effectively competing with other therapies;
- enforcing and defending intellectual property rights and claims; and
- raising sufficient funds to support regulatory approval and commercialization activities.

Many of these risks are beyond our control, including the risks related to clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any future collaborator. If we or any collaborator are unable to develop, receive regulatory approval for, or successfully commercialize XEN1101 for our initial or potential additional indications, or if we experience delays as a result of any of these risks or otherwise, our business could be materially harmed.

In addition, of the large number of drugs in development in the pharmaceutical industry, only a small percentage result in the submission of an NDA to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval for XEN1101 for any indication, any such approval may be subject to limitations on the indications or uses or patient populations for which we may market XEN1101. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we cannot ensure that we will successfully develop or commercialize XEN1101 for any indication.

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 product candidates yet fail to yield viable product candidates for clinical development or commercialization. Such failure may occur for many reasons, including that 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/or 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 if 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.

Results of pre-clinical studies and/or earlier clinical trials may not be predictive of the results of later-stage clinical trials and the results of our clinical trials may not satisfy regulatory requirements and we may experience delays or unexpected difficulties in obtaining regulatory approval.

The results of pre-clinical studies, either generated by us, by our CROs or by other third parties from which we have in-licensed or acquired a product candidate, may not be predictive of results in clinical testing. Moreover, pre-clinical results can often be difficult to compare across different studies for a variety of reasons, including differences in experimental protocols and techniques, personnel, equipment and other factors, which may make the pre-clinical results less reliable and predictive of clinical trial results. In addition, published clinical data or case reports from third parties or early clinical trial data of our product candidates may not be predictive of the results of later-stage clinical trials. Interpretation of results from early, usually smaller, studies that suggest a clinically meaningful response in some patients, requires caution. Results from later stages of clinical trials enrolling more patients may fail to show the desired safety and efficacy results or otherwise fail to be consistent with the results of earlier trials of the same product candidate. Later clinical trial results may not replicate earlier clinical trials for a variety of reasons, including differences in trial design, different trial endpoints (or lack of trial endpoints in exploratory studies), patient population, number of patients, patient selection criteria, trial duration, drug dosage and formulation and lack of statistical power in the earlier studies. These uncertainties are enhanced where the diseases or disorders under study lack established clinical endpoints, validated measures of efficacy, as is often the case with disorders for which no drugs have been developed previously and where the product candidates target novel mechanisms.

Further, our product candidates may not be approved even if they achieve their primary endpoint in our Phase 3 clinical trials. The FDA, EMA or foreign regulatory authorities may disagree with our trial design and our interpretation of data from pre-clinical studies and clinical trials or require additional data. In addition, any of these regulatory authorities may change its requirements for the approval of a product candidate even after reviewing and providing comments or advice on a protocol for a pivotal clinical trial that, if successful, would potentially form the basis for an application for approval by the FDA, EMA or another foreign regulatory authority. For example, the FDA may refuse to accept our planned NDA for substantive review or may conclude after review of our data that our application is insufficient to obtain regulatory approval. If the FDA does not approve our planned NDA, it may require that we conduct additional clinical, nonclinical or manufacturing studies before it will reconsider our application. Depending on the extent of these or any other studies required by FDA or another regulatory authority, approval of an NDA or equivalent filing may be significantly delayed or may require us to expend more resources than we have available. Furthermore, applicable regulatory authorities may also approve our product candidates for a narrower indication or population than we request or may grant approval contingent on the performance of costly post-marketing commitments.

Interim, initial, "top-line" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or top-line data from our pre-clinical studies and clinical trials, which are based on preliminary analyses of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular pre-clinical study or clinical trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the top-line or preliminary results that we report may differ from future results of the same studies or trials, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Top-line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, top-line data should be viewed with caution until the final data are available.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and could have a material adverse effect on the success of our business. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure. If the interim, topline or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, results of operations, prospects or financial condition. Further, disclosure of interim, top-line or preliminary data by us or by our competitors could result in volatility in the price of our common shares.

Clinical trials may fail to demonstrate adequately the safety and efficacy of our, or our collaborators', product candidates at any stage of clinical development. Terminating the development of any of our, or our collaborators', product candidates could materially harm our business and the market price of our common shares.

Our and our collaborators' clinical product candidates, which include XEN1101 and NBI-921352 (being developed by our collaborator Neurocrine Biosciences), along with product candidates we expect to enter clinical development, which include our pre-clinical compounds, are in varying stages of development and will require substantial clinical development, testing and regulatory approval prior to commercialization.

Before obtaining regulatory approvals for the commercial sale of our product candidates, we, or our collaborators, must demonstrate through lengthy, complex and expensive pre-clinical testing and clinical trials that each product candidate is both safe and effective for use in each target indication. Failure can occur at any time during the clinical trial process. Clinical trials often fail to demonstrate safety and efficacy of the product candidate studied for the target indication. Most product candidates that commence clinical trials are never approved as products. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. In addition to the safety and efficacy trials of any product candidate, clinical trial failures may result from a multitude of factors including flaws in trial design, dose selection, statistical analysis plan, placebo effect, patient enrollment criteria, patient compliance and trial execution. Data obtained from trials and studies are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may delay, limit or prevent regulatory approval. Failure of a clinical trial due to any of these reasons could materially harm our business and the market price of our common shares.

In the case of some of our and our collaborators' product candidates, we and our collaborators are seeking to develop treatments for certain diseases or disorders for which there is relatively limited clinical experience, and clinical trials may use novel endpoints and measurement methodologies or subjective patient feedback, which adds a layer of complexity to these clinical trials and may delay regulatory approval. Negative or inconclusive results from our, or our collaborators', clinical trials could lead to a decision or requirement to conduct additional pre-clinical testing or clinical trials or result in a decision to terminate the continued development of a product candidate. For example, in October 2021, we released topline data from our Phase 2b X-TOLE clinical trial of XEN1101 in adult patients with focal epilepsy. In addition, in November 2023, we released topline data from our Phase 2 X-NOVA clinical trial of XEN1101 in patients with MDD. There can be no assurance that our ongoing XEN1101 Phase 3 epilepsy clinical trials or any other future Phase 3 clinical trials will demonstrate adequate efficacy and safety results and that we will be able to obtain regulatory approval of XEN1101. Any of the foregoing outcomes would materially and adversely impact our business, product candidate pipeline and future prospects.

If our, or our collaborators', product candidates are not shown to be both safe and effective in clinical trials, such product candidates will be unable to obtain regulatory approval or be successfully commercialized. In addition, our, or our collaborators', failure to demonstrate positive results in clinical trials in any indication for which we, or our collaborators, are developing clinical product candidates could adversely affect development efforts in other indications. In such case, we would need to develop other compounds and conduct associated pre-clinical testing and clinical trials, as well as potentially seek additional financing, all of which would have a material adverse effect on our business, growth prospects, operating results, financial condition and results of operations.

We, or our collaborators, may find it difficult to enroll patients in our clinical trials which could delay or prevent the successful completion of clinical trials of our product candidates.

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

- severity of the disease or disorder under investigation;
- design of the study protocol;
- size of the patient population and geographic dispersion;
- identification of patients;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study;
- our ability to recruit clinical trial investigators with the appropriate competencies, staff and experience;
- proximity and availability of clinical trial sites for prospective patients;
- availability of competing therapies and clinical trials;
- efforts to facilitate timely enrollment in clinical trials; and
- patient referral practices of physicians.

Our and our collaborators' clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites.

Our and our collaborators' inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Delays in patient enrollment may result in increased costs, affect the timing or outcome of the planned clinical trials, affect product candidate development and approval process and jeopardize our ability to seek and obtain the regulatory approval required to commence product sales and generate revenue, any of which could cause the value of our company to decline and limit our ability to obtain additional financing if needed.

Our success also depends on the collective performance, contributions, and expertise of the personnel who manage our clinical trial sites. There is significant competition for qualified personnel, particularly those with higher educational degrees, in the biopharmaceutical and related services industries. Increased personnel turnover and labor shortages facing the biopharmaceutical services industry could have a negative impact on the third parties we rely on to execute our clinical trials. While we seek to choose trial sites with adequate staffing support, we cannot be certain that personnel turnover or the broader labor market dynamics in this industry will not negatively impact our trial sites. If our sites are negatively impacted by these factors, our ability to enroll our clinical trials in a timely fashion may be hindered and might negatively affect our business, development timelines, and financial condition.

We, or our collaborators, may incur unexpected costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our, or our collaborators', product candidates.

To obtain the requisite regulatory approvals to commercialize any of our product candidates, we, or our collaborators, must demonstrate through extensive pre-clinical studies and clinical trials that our, or our collaborators', product candidates are safe and effective in humans. We, or our collaborators, may experience delays in completing our, or our collaborators', clinical trials or pre-clinical studies, and initiating or completing additional clinical trials or pre-clinical studies, including as a result of regulators not allowing or delay in allowing clinical trials to proceed under an IND, or not approving or delaying approval for any clinical trial grant or similar approval we need to initiate a clinical trial. We, or our collaborators, may also experience numerous unforeseen events during our clinical trials that could delay or prevent our, or our collaborators', ability to complete development for a product candidate, or receive marketing approval or commercialize the product candidates we, or our collaborators, develop, including:

- delay or failure in obtaining the necessary approvals from regulators or institutional review boards, or IRBs, in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;
- inability to reach agreement with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites, or the breach of such agreements;
- we may experience challenges or delays in recruiting principal investigators or study sites to lead our clinical trials;
- side effects or adverse events in study participants presenting an unacceptable safety risk;
- failure of third-party contractors, such as CROs, or investigators to comply with regulatory requirements, including good clinical practices, or GCPs;
- difficulty in having patients complete a trial, adhere to the trial protocol, or return for post-treatment follow-up;
- the number of subjects or patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be insufficient or slower than we anticipate, and the number of clinical trials being conducted at any given time may be high and result in fewer available patients for any given clinical trial, or patients may drop out of these clinical trials at a higher rate than we anticipate;
- clinical sites deviating from trial protocol or dropping out of a trial;
- we may have to amend clinical trial protocols submitted to regulatory authorities or conduct additional studies to reflect changes in regulatory requirements or guidance, which it may be required to resubmit to an IRB and regulatory authorities for re-examination;
- challenges or delays with accessing certain species of animals to complete our pre-clinical studies;
- problems with investigational medicinal product storage, stability and distribution;
- our inability to manufacture, or obtain from third parties, adequate supply of drug substance or drug product sufficient to complete our pre-clinical studies and clinical trials, including supply chain issues resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- a requirement to undertake and complete additional pre-clinical studies to generate data required to initiate clinical development or to support the continued clinical development of a product candidate or submission of an NDA or equivalent;
- unforeseen disruptions, caused by man-made or natural disasters, public health pandemics or epidemics, civil unrest or military conflict, or other business interruptions; and
- governmental or regulatory delays and changes in regulatory requirements, policy and guidelines.

These risks and uncertainties could impact any of our, or our collaborators', clinical programs and any of the clinical, regulatory or operational events described above could change our, or our collaborators', planned clinical and regulatory activities. Challenges in enrolling and retaining patients in our clinical trials, including in our XEN1101 Phase 3 epilepsy clinical trials, whether as a result of pandemics, geopolitical events, or for any other reasons, may further delay the trials or cause them to be discontinued.

The results of any Phase 3 or other pivotal clinical trials may not be adequate to support marketing approval. These clinical trials are lengthy and usually involve many hundreds to thousands of patients. Clinical trials can also be lengthy due to the challenge of identifying patients. Even if patients are successfully identified, they may fail screening criteria, including baseline seizure burden for epilepsy clinical trials, and, as a result, not be enrolled in the trial. Any challenges associated with identifying, screening and/or enrolling patients in our trials may extend the time needed to complete our clinical trials or require additional sites to be initiated in order to achieve target enrollment numbers and to complete our clinical trials, which may increase the cost of our operations and/or delay the timing of our regulatory approval. In addition, if the FDA, EMA or another foreign regulator disagrees with our, or our collaborators', choice of the key testing criterion, or primary endpoint, or if the results for the primary endpoint are not robust or significant relative to the control group of patients not receiving the experimental therapy, or our statistical analysis is inconclusive, such regulator may refuse to approve our product candidate in the region in which it has jurisdiction. The FDA, EMA or other foreign regulators also may require additional clinical trials as a condition for approving any of these product candidates.

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

Additionally, changes in applicable regulatory requirements and guidance may occur and we may need to amend clinical trial protocols to reflect these changes or to include additional objectives that could yield important scientific information critical to our overall development strategy. The protocol amendment process often requires review and approval by several review bodies, including regulatory agencies and scientific, regulatory and ethics boards and IRBs which may affect timely completion of a clinical trial. Further, these protocol amendments may not be accepted by the review bodies in the form submitted, or at all, which may impact costs, timing or successful completion of a clinical trial.

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

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following regulatory approval, if obtained.

Undesirable side effects caused by any of our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, EMA or comparable foreign regulatory authorities.

Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. For example, while adverse events in our X-TOLE and X-NOVA clinical trials were generally mild or moderate in severity, there can be no guarantee that we will observe a similar tolerability profile of XEN1101 in our ongoing Phase 3 epilepsy or other clinical trials or in other future clinical trials. Many compounds that initially showed promise in clinical or earlier-stage testing are later found to cause undesirable or unexpected side effects that prevented further development of the compound.

If unacceptable side effects arise in the development of our product candidates, we, the FDA, EMA or comparable foreign regulatory authorities, the IRBs, or independent ethics committees at the institutions in which our trials are conducted, could suspend, limit or terminate our clinical trials, or the independent safety monitoring committee could recommend that we suspend, limit or terminate our trials, or the FDA, EMA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-emergent side effects that are deemed to be drug-related could delay recruitment of clinical trial subjects or cause subjects that enroll in our clinical trials to discontinue participation in our clinical trials. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We may need to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in harm to patients that are administered our product candidates. Any of these occurrences may adversely affect our business, financial condition and prospects significantly.

Moreover, clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects.

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

As product candidates are developed through pre-clinical to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulations, are altered along the way in an effort to optimize products, processes and results, to extend patent protection and/or to target different populations. For example, we have developed a pediatric formulation for NBI-921352 that was included in the license to Neurocrine Biosciences. Any of these changes could cause our product candidates to perform differently and not provide the same drug exposure profile in children and/or cause side effects different to those observed with the same formulation in adults or with other formulations. Unexpected changes in the performance of a new formulation may affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of additional bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs and/or delay or jeopardize approval of our product candidates and/or jeopardize our, or our collaborators', ability to commence product sales and generate revenue.

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

The regulatory approval process is expensive and the time required to obtain approval from the FDA, EMA or other foreign regulatory authorities in other jurisdictions to sell any product is uncertain and may take years. Whether regulatory approval will be granted is unpredictable and depends upon numerous factors, including the substantial discretion of the regulatory authorities. Approval policies, regulations, or the type and amount of pre-clinical and clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. Moreover, pre-clinical and clinical data are often susceptible to varying interpretations and analyses, and even if the pre-clinical studies show promising results and clinical trials are successfully completed, we cannot guarantee that the FDA, EMA or other foreign regulatory authorities in other jurisdictions will interpret the results as we do, and more trials, manufacturing-related studies or non-clinical studies could be required before we submit our product candidates for approval. Many companies that have believed their product candidates performed satisfactorily in pre-clinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. To the extent that the results of our studies and trials are not satisfactory to the FDA, EMA or other foreign regulatory authorities in other jurisdictions for support of a marketing application, approval of our product candidates may be significantly delayed, or we may be required to expend significant additional resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates. It is also possible that none of our existing product candidates or any of our future product candidates will ever obtain regulatory approval, even if we expend substantial time and resources seeking such approval.

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

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

- we, or our collaborators, may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA, EMA or other foreign regulatory authorities may disagree with our, or our collaborators', interpretation of data from pre-clinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA, or other submission or to obtain regulatory approval in the U.S. or elsewhere;
- the FDA, EMA or other foreign regulatory authorities may fail to approve the manufacturing processes, controls or facilities of third-party manufacturers with which we, or our collaborators, contract for clinical and commercial supplies;
- the pre-approval inspections of Xenon, manufacturing, clinical sites, pre-clinical or clinical service providers, conducted by regulatory authorities may identify errors or omissions that may result in the product candidate not being approved; and
- the approval policies or regulations of the FDA, EMA or other foreign regulatory authorities may significantly change in a manner rendering our, or our collaborators', clinical data insufficient for approval.

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

In addition, the FDA, EMA or other foreign regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For instance, the regulatory landscape related to clinical trials in the EU recently evolved. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repealed the EU Clinical Trials Directive, became applicable on January 31, 2022. The implementation of the CTR also includes the implementation of the Clinical Trials Information System, or CTIS, a new clinical trial portal and database that will be maintained by the European Medicines Agency, or EMA, in collaboration with the European Commission and the EU Member States. The objectives of the CTR include consistent rules for conducting trials throughout the EU, consistent data standards and adverse events listing, and consistent information on the authorization status. Information on the conduct and results of each clinical trial carried out in the EU will be made publicly available. The CTR authorizes EU Member States to regulate certain aspects of clinical trials at the national level. To the extent an EU Member State where we plan to conduct any of our clinical trials is slow to adopt CTIS or implements other regulatory changes at the national level, or technical issues are encountered with the CTIS system and/or process, our clinical trial may be delayed in such EU Member State, and our costs may be increased. The main legislation that applies to clinical trials in the United Kingdom, or UK, is the UK Medicines for Human Use (Clinical Trials) Regulations 2004, which transposes the EU Clinical Trials Directive into domestic law. The UK has implemented the Integrated Research Application System, which allows a single application to be reviewed by both the Medicines and Healthcare products Regulatory Agency and a research ethics committee at the same time. Requirements and obligations that relate to the conduct of clinical trials in the UK remain largely aligned with the EU position. Complying with changes in regulatory requirements in different jurisdictions can result in additional costs, delay our clinical development plans, or expose us to greater liability if we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans, including our XEN1101 Phase 3 epilepsy clinical trials, may be impacted.

Additionally, because there may be approved treatments for some of the diseases or disorders for which we may seek approval, in order to receive regulatory approval, we may need to demonstrate in clinical trials that the product candidates we develop to treat those diseases or disorders are not only safe and effective, but may need to be compared to existing products, which may make it more difficult for our product candidates to receive regulatory approval or adequate reimbursement.

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

Sales of our approved products, if any, will be subject to the regulatory requirements governing marketing approval in the countries in which we obtain regulatory approval, and we plan to seek, ourselves or with collaborators, regulatory approval to commercialize our product candidates in North America, the EU and in additional foreign countries. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries and regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others. For example, approval in the U.S. by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by the FDA, EMA or regulatory authorities in other countries. Approval procedures vary among jurisdictions and can be lengthy and expensive, and involve requirements and administrative review periods different from, and potentially greater than, those in the U.S., including additional pre-clinical studies or clinical trials. Even if our product candidates are approved, regulatory approval for any product may be withdrawn by the regulatory authorities in a particular jurisdiction. We do not have experience in obtaining regulatory approval in international markets. If we, or our collaborators, fail to comply with regulatory requirements or to obtain and maintain required approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Although orphan drug designation has been granted in the United States and Europe to NBI-921352 for the treatment of SCN8A-DEE, we may not be able to realize any value from such designations.

NBI-921352, being developed by our collaborator Neurocrine Biosciences, has received orphan drug designation from the FDA and orphan medicinal product designation was granted by the European Commission for the treatment of SCN8A-DEE. Currently, orphan drug designation provides market exclusivity in the U.S. and the EU for seven years and ten years, respectively, if a product is the first such product approved for such orphan indication. In the EU, for orphan medicines, a valid and completed Pediatric Investigation Plan, or PIP, could qualify the sponsor for a two-year marketing exclusivity extension to the ten-year marketing exclusivity which is granted at the time of review of the orphan medicinal designation. The orphan drug market exclusivity does not, however, pertain to indications other than those for which the drug was specifically designated in the approval, nor does it prevent other types of drugs from receiving orphan designations or approvals in these same indications. Further, even after an orphan drug is approved, the FDA can subsequently approve a drug with similar chemical structure for the same condition if the FDA concludes that the new drug is clinically superior to the orphan product or a market shortage occurs. Orphan drug designation does not provide the drug any advantage in the regulatory review or approval process other than potential fee reductions, nor does such designation increase the likelihood that the drug will receive marketing approval.

In *Catalyst Pharms., Inc. v. Becerra*, 14 F.4th 1299 (11th Cir. 2021), the court disagreed with the FDA's longstanding position that the orphan drug exclusivity only applies to the approved use or indication within an eligible disease. This decision created uncertainty in the application of the orphan drug exclusivity in the U.S. On January 24, 2023, the FDA published a notice in the Federal Register to clarify that while the FDA complied with the court's order in Catalyst, the FDA intends to continue to apply its longstanding interpretation of the regulations to matters outside of the scope of the Catalyst order – that is, the FDA will continue tying the scope of orphan-drug exclusivity to the uses or indications for which a drug is approved, which permits other sponsors to obtain approval of a drug for new uses or indications within the same orphan designated disease or condition that have not yet been approved. It is unclear how future litigation, legislation, agency decisions and administrative actions will impact the scope of the orphan drug exclusivity.

In the EU, orphan exclusivity may be reduced to six years if the drug no longer satisfies the original designation criteria or can be lost altogether if the marketing authorization holder consents to a second orphan drug application or cannot supply enough drug, or when a second applicant demonstrates its drug is "clinically superior" to the original orphan drug.

Although the FDA has granted rare pediatric disease, or RPD, designation to NBI-921352 for the treatment of SCN8A-DEE, we may not be able to realize any value from such designation.

NBI-921352, being developed by our collaborator Neurocrine Biosciences, has received RPD designation for the treatment of SCN8A-DEE. The FDA defines a "rare pediatric disease" as a disease that affects fewer than 200,000 individuals in the U.S. primarily under the age of 18 years old. Under the FDA's RPD priority review voucher program, upon the approval of an NDA or a biologics license application, BLA, for the treatment of an RPD, the sponsor of such application would be eligible for a priority review voucher that can be used to obtain priority review for a subsequent NDA or BLA. There is no assurance Neurocrine Biosciences will receive a RPD priority review voucher or that use of the priority review voucher will result in a faster review or approval for a subsequent marketing application. It is possible that even if Neurocrine Biosciences obtains approval for NBI-921352 in SCN8A-DEE and qualifies for such a priority review voucher, the program may no longer be in effect at the time of approval of this product candidate. Also, although priority review vouchers may be freely sold or transferred to third parties, there is no guarantee that we will be able to realize any value if we or any of our collaborators were to sell a priority review voucher to a third-party. In addition, Congress extended FDA authorization to designate RPDs through September 30, 2024 and award RPD priority review vouchers through September 30, 2026. RPD designation does not provide the drug any advantage in the regulatory review or approval process other than potential fee reductions, and priority review vouchers, nor does such designation increase the likelihood that the drug will receive marketing approval.

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

We face an inherent risk of product liability as a result of the clinical testing of our product candidates, and we will face an even greater risk if we commercialize any product candidates. For example, we may be sued if any of our product candidates, including any that are developed in combination with other therapies, allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Claims could also be asserted under state or provincial consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. There is also risk that third parties we have agreed to indemnify could incur liability. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates or any resulting products;
- injury to our reputation;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- the inability to commercialize our product candidates; and
- a decline in the market price of our common shares.

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

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

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

We do not have a sales or marketing infrastructure and, as a company, have no sales, marketing or distribution experience. Our strategy involves building our own commercial infrastructure to selectively commercialize future products in certain commercial markets which will be expensive and time consuming. For certain products, including XEN1101, and/or specific commercial markets, we evaluate commercial partners from time to time. In some cases, we may seek to retain the right to participate in the future development and commercialization of such products if we believe such involvement would advance our business. We cannot be certain that we will be successful in consummating any such commercial partnerships or, if consummated, whether such partnerships will be successful.

To develop internal sales, distribution and marketing capabilities in the U.S., we will have to invest significant amounts of financial and management resources, some of which will need to be committed prior to any confirmation that any of our product candidates will be approved. We have no prior experience as a company in the marketing, sale and distribution of biopharmaceutical products and there are significant risks involved in building and managing a commercial organization. For any future products for which we decide to perform sales, marketing and distribution functions ourselves, we could face a number of additional risks, including:

- the maintenance of existing or the establishment of new supply arrangements with third-party logistics providers and secondary packagers;
- the maintenance of existing or the establishment of new scaled production arrangements with third-party manufacturers to obtain finished products that are appropriately packaged for sale;
- a continued acceptable safety profile following any marketing approval;
- our ability to recruit and retain adequate numbers of qualified sales and marketing personnel or develop alternative sales channels;
- the ability of our products to secure acceptance from physicians, healthcare providers, patients, third-party payers and the medical community including identifying an adequate number of physicians and patients;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines;
- unforeseen costs and expenses associated with creating and maintaining an independent sales and marketing organization; and
- our ability to compete with other therapies.

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

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

Any of our product candidates for which we, or any existing or future collaborators, obtain regulatory approval, as well as the manufacturing processes, post-approval studies, labeling, advertising and promotional activities for such product, among other things, will be subject to ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. We and our contract manufacturers will also be subject to user fees and periodic inspection by the FDA and other regulatory authorities to monitor compliance with these requirements and the terms of any product approval we may obtain. In addition, our product candidates may receive schedule classifications under the Controlled Substances Act of 1970 (or scheduling classifications under similar legislation outside of the U.S.) which will result in additional complexity and may result in delays and restrictions with respect to manufacturing, supply chain, licensing, import/export and distribution.

Even if a product is approved, the FDA or another applicable regulatory authority, as the case may be, may limit the indications for which the product may be marketed, require extensive precautions and warnings on the product labeling or require expensive and time-consuming post-approval commitments including clinical trials or onerous risk management activities, including Risk Evaluation and Mitigation Strategies, or REMS, in the U.S. as conditions of approval to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug.

For any approved product, we, or our collaborators, will need to ensure continued compliance with extensive regulations and requirements regarding the manufacturing processes, labeling, packaging, serialization, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product. These requirements include submissions of safety and other post-approval information and reports, as well as continued compliance with current good manufacturing practices, or cGMP, good distribution practices, or GDP, and current good clinical practices, or cGCP, for any clinical trials that we, or our collaborators, are required to conduct post-approval.

Post-approval discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or other problems with our product or with third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, amongst other things, restrictions on the labeling or marketing, withdrawals, consent decrees, clinical holds, post-approval requirements or restrictions, recalls, fines, warning letters, injunctions, penalties, exclusions from federal healthcare programs, seizures and/or detentions, among other consequences and adverse actions. Occurrence of any of the foregoing could have a material and adverse effect on our business and results of operations.

In addition, prescription drugs may be promoted only for the approved indications in accordance with the approved label. The FDA, EMA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label use may be subject to significant liability. However, physicians may, in their independent medical judgment, prescribe legally available products for off-label uses. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA, EMA and other foreign regulators do restrict manufacturers' communications on the subject of off-label use of their products.

To the extent we develop and commercialize product candidates that contain or are considered controlled substances, any failure by us or our CROs, CMOs and other contractors to comply with controlled substance laws and regulations, may adversely affect the results of our business operations and our financial condition.

We may in the future develop product candidates that are considered controlled substances in multiple jurisdictions, such as the U.S., Canada, and the EU, which will expose us to additional controlled substance regulatory requirements in each applicable jurisdiction where we engage in regulated activities, including storage, manufacture, research, clinical trials, import, and export, among other activities. For example, obtaining and maintaining the necessary registrations may result in delay of the importation, manufacturing or distribution of our controlled substance product candidates and may extend our anticipated timelines for clinical trials we run.

Controlled substances or scheduled substances are regulated by the DEA under the CSA. The DEA regulates compounds as Schedule I, II, III, IV or V substances. Pharmaceutical products approved for use in the U.S. may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse among such substances.

Scheduling determinations by the DEA are dependent on FDA approval of a substance or a specific formulation of a substance. This scheduling determination will be dependent on FDA approval and the FDA's recommendation as to the appropriate schedule, which may introduce a delay into the approval and any potential rescheduling process. There can be no assurance that the DEA will make a favorable scheduling decision. Substances that are Schedule II, III, IV or V controlled substances at the federal level may also require scheduling determinations under state laws and regulations, as well as similar foreign controlled substances regulations, if applicable. If approved by the FDA, a number of post-approval activities involving controlled substances will be subject to regulation by the DEA, including DEA regulations relating to registration and inspection of facilities, manufacturing, storage, distribution and physician prescription procedures, among others. Furthermore, failure of our contractors, such as our CROs and CMOs, to maintain compliance with the CSA during development and/or commercialization, as applicable, can result in a material adverse effect on our business, financial condition and results of operations.

Individual U.S. states and countries outside of the U.S. have also established controlled substance laws and regulations. Those laws and regulations, including state-controlled substances laws that often but not necessarily mirror federal law, may separately schedule our product candidates. Complying with different controlled substances requirements across different jurisdictions can increase the cost of our operations and expose us to additional liabilities.

Even if we obtain marketing approval for our product candidates, the presence of a controlled substance in the product candidate may lead to adverse publicity or public perception regarding our current or future product candidates.

If our product candidates that are subject to controlled substances regulation are approved for commercial sale, adverse publicity or public perception of controlled substances in general or other controlled substances could negatively impact market acceptance or consumer perception of our product candidates. We may face limited adoption if clinicians or patients are unwilling to try a novel treatment that contains a controlled substance. Any adverse publicity associated with illness or other adverse effects resulting from patients' use or misuse of our or similar therapies distributed by other companies could have a material adverse impact on our business, prospects, financial condition and results of operations.

Future adverse events and research in controlled substances that are present in the product candidates could also result in greater governmental regulation, stricter labeling requirements and potential regulatory delays in the testing or approvals of our product candidates. Any increased scrutiny could delay or increase the costs of obtaining regulatory approval for our product candidates.

Any product candidates we develop may become subject to unfavorable third-party coverage and reimbursement practices, as well as pricing regulations.

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

There is significant uncertainty related to third-party payer coverage and reimbursement of newly approved products. Within the U.S., coverage and reimbursement varies from one third party payer to another. One third-party payer's determination to provide coverage for a product candidate does not assure that other payers will also provide coverage for the product candidate. As a result, the coverage determination process is often time-consuming and costly. Factors payers consider in determining reimbursement are based on whether the product is: (i) a covered benefit under its health plan; (ii) safe, effective and medically necessary; (iii) appropriate for the specific patient; (iv) cost-effective; and (v) neither experimental nor investigational. We may be required to provide scientific and clinical support for the use of our products to each third-party payer separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

As federal and state governments implement additional healthcare cost containment measures, including measures to lower prescription drug pricing, we cannot be sure that our products, if approved, will be covered by private or public payers, and if covered, whether the reimbursement will be adequate or competitive with other marketed products. Actions by federal and state governments and health plans may put additional downward pressure on pharmaceutical pricing and healthcare costs, which could negatively impact coverage and reimbursement for our products if approved, our revenue, and our ability to compete with other marketed products and to recoup the costs of our research and development.

Additionally, net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payers and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. In order to obtain and maintain acceptable reimbursement levels and access for patients at copay levels that are reasonable and customary, we may have to offer discounts or rebates from list prices or to implement other unfavorable pricing modifications. We cannot be sure that reimbursement will be available for any product candidate that we commercialize and, if reimbursement is available, the level of reimbursement.

Outside the U.S., the commercialization of therapeutics is generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the countries of the EU, medical product prices are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after a product receives marketing approval. To obtain reimbursement or pricing approval in some countries, we, or our collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In general, product prices under such systems are substantially lower than in the U.S. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we, or our collaborators, are able to charge for our product candidates. Accordingly, in markets outside the U.S., the reimbursement for our products may be reduced compared with the U.S. and may be insufficient to generate commercially reasonable revenue and profits.

Some of our or our collaborators' target patient populations may be in orphan or niche indications, such as SCN8A-DEE. In order for therapies that are designed to treat smaller patient populations to be commercially viable, the pricing, coverage and reimbursement for such therapies needs to be higher, on a relative basis, to account for the lack of volume. Accordingly, we or our collaborators may need to implement pricing, coverage and reimbursement strategies for any approved product that accounts for the smaller potential market size. If we or our collaborators are unable to establish or sustain coverage and adequate reimbursement for our or our collaborators' current and any future products from third-party payers or the government, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those products.

Healthcare and other reforms may increase the difficulty and cost for us to commercialize any products that we, or our collaborators, develop and affect the prices we may obtain.

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

For example, in 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively, the PPACA, was enacted and includes measures that have significantly changed the way healthcare is financed by both governmental and private insurers. Beyond the ACA, there are ongoing and widespread health care reform efforts, a number of which have focused on regulation of prices or payment for drug products. Drug pricing and payment reform was a focus of the Trump Administration and has been a focus of the Biden Administration. For example, federal legislation enacted in 2021 eliminates a statutory cap on Medicaid drug rebate program rebates effective January 1, 2024. As another example, the Inflation Reduction Act (IRA) of 2022 contains various drug price negotiation, inflationary rebate, and pricing provisions with varying implementation dates. The IRA allows the federal government to negotiate a maximum fair price for certain high-priced single-source Medicare drugs, impose penalties and excise tax for manufacturers that fail to comply with the drug price negotiation requirements, require inflation rebates for all Medicare Part B and Part D drugs (with limited exceptions) if their drug prices increase faster than inflation, and redesigns Medicare Part D to reduce out-of-pocket prescription drug costs for beneficiaries, among other changes. The impact of the IRA on our business and the broader pharmaceutical industry remains uncertain as implementation is ongoing. As another example, in 2022, subsequent to the enactment of the IRA, the Biden administration released an executive order directing the HHS to report on how the Center for Medicare and Medicaid Innovation ("CMMI") could be leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. The report was issued in 2023 and proposed various models that CMMI is currently developing which seek to lower the cost of drugs, promote accessibility and improve quality of care. These changes or other changes could affect the market conditions for our products. We expect continued scrutiny on drug pricing and government price reporting from Congress, agencies, and other bodies.

Further, a number of states have enacted state drug price transparency and reporting laws that could substantially increase our compliance burdens and expose us to greater liability under such state laws if and when we have marketed products. These and other health reform measures that are implemented may have a material adverse effect on our operations.

Healthcare reform efforts have been and may continue to be subject to scrutiny and legal challenge. For example, with respect to the PPACA, tax reform legislation was enacted that eliminated the tax penalty established for individuals who do not maintain mandated health insurance coverage beginning in 2019 and, in 2021, the U.S. Supreme Court dismissed the latest judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the PPACA. As another example, revisions to regulations under the federal anti-kickback statute would remove protection for traditional Medicare Part D discounts offered by pharmaceutical manufacturers to pharmacy benefit managers and health plans. Pursuant to court order, the removal was delayed and recent legislation imposed a moratorium on implementation of the rule until January 2032. As another example, the IRA drug price negotiation program has been challenged in litigation filed by various pharmaceutical manufacturers and industry groups.

We are unable to predict the future course of federal or state healthcare legislation in the U.S. Any further changes in the law or regulatory framework could reduce our ability to generate revenue in the future or increase our costs, either of which could have a material and adverse effect on our business, financial condition and results of operations. The continuing efforts of the government and other third-party payers to contain or reduce costs of healthcare and/or impose price controls may adversely affect the demand for our product candidates, if approved, and our ability to achieve or maintain profitability.

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

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

In addition, other broader legislative changes have been adopted that could have an adverse effect upon, and could prevent, our products' commercial success. For example, the Budget Control Act of 2011, as amended, resulted in the imposition of reductions in Medicare (but not Medicaid) payments to providers in 2013 and remains in effect through 2032 unless additional Congressional action is taken. Any significant spending reductions affecting Medicare, Medicaid or other publicly funded or subsidized health programs that may be implemented and/or any significant taxes or fees that may be imposed on us could have an adverse impact on our results of operations.

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

Risks Related to Our Dependence on Third Parties

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

We have no control over the resources, time and effort that our collaborators may devote to our programs and limited access to information regarding or resulting from such programs. We are dependent on our collaborators, including Neurocrine Biosciences, to fund and conduct the research and any clinical development of product candidates under our agreements with each of them, and for the successful regulatory approval, marketing and commercialization of one or more of such products or product candidates. Such success will be subject to significant uncertainty.

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

- a collaborator may shift its priorities and resources away from our programs due to a change in business strategies, or a merger, acquisition, sale or downsizing of its company or business unit;
- a collaborator may cease development in therapeutic areas which are the subject of our strategic alliances;

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

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

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

In the ordinary course, we engage with other biotechnology and pharmaceutical companies to discuss potential in-licensing, out-licensing, alliances and other strategic transactions. The advancement of our product candidates and development programs and the potential commercialization of our current and future product candidates will require substantial additional cash to fund expenses. Additionally, there are certain jurisdictions where a collaborator may be able to realize the market potential of our product candidates better than us. For these or other reasons, we may decide to collaborate with additional pharmaceutical and biotechnology companies with respect to development and potential commercialization.

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

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

- the development of certain of our current or future product candidates may be terminated or delayed;
- our cash expenditures related to development or commercialization of any such product candidates would increase significantly and we may need to seek additional financing sooner than expected;

- we may be required to hire additional employees or otherwise develop expertise, such as clinical, regulatory, sales and marketing expertise, some of which we do not currently have;
- we may delay commercialization or reduce the scope of any sales or marketing activities;
- we will bear all of the risk related to the development or commercialization of any such product candidates; and
- the competitiveness of any product that is commercialized could be reduced.

Our reliance on third parties to manufacture our product candidates may increase the risk that we will not have sufficient quantities of our product candidates, raw materials, APIs or drug products when needed or at an acceptable cost.

We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we lack the resources and the capabilities to do so. As a result, we currently rely on third parties for the manufacture and supply of the active pharmaceutical ingredients, or APIs, in our product candidates and the final drug product formulation for all of our product candidates that are being used in our clinical trials and pre-clinical studies as well as packaging, labelling and distribution of clinical trial supplies. Our current strategy is to outsource all manufacturing of our product candidates to third parties.

In addition, we rely on our collaborators, either directly or through CMOs, to manufacture product candidates licensed to them or to work with CMOs to produce sufficient quantities of materials required for the manufacture of our product candidates for pre-clinical testing and clinical trials and intend to do so for the commercial manufacture of our products. If we, or our collaborators, are unable to arrange for such third-party manufacturing sources, or fail to do so on commercially reasonable terms, we, or our collaborators, may not be able to successfully produce sufficient supply of a product candidate or we, or our collaborators, may be delayed in doing so. Such failure or substantial delay could delay our clinical trials and materially harm our business. The manufacture of biopharmaceutical products is complex and requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. The process of manufacturing our product candidates is susceptible to product loss due to contamination, equipment failure or improper installation or operation of equipment, vendor or operator error, contamination and inconsistency in yields, variability in product characteristics and difficulties in scaling the production process. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects and other supply disruptions. If microbial, viral or other contaminations are discovered in our product candidates or in the third-party manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. Any adverse developments affecting manufacturing operations for our product candidates, if any are approved, may result in shipment delays, inventory shortages, lot failures, product withdrawals or recalls, or other interruptions in the supply of our products. We may also have to take inventory write-offs and incur other charges and expenses for products that fail to meet specifications, undertake costly remediation efforts or seek more costly manufacturing alternatives.

Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including reliance on these third parties for regulatory compliance and quality control and assurance, volume production, the possibility of breach of the manufacturing agreement by the third-party because of factors beyond our control (including a failure to synthesize and manufacture our product candidates in accordance with our product specifications), the impact of industry consolidation, including business combinations involving such third parties, and the possibility of termination or nonrenewal of the agreement by the third-party at a time that is costly or damaging to us. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

In addition, we typically order raw materials, APIs and drug product and services on a purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements with any commercial manufacturer. There is no assurance that we will be able to timely secure needed supply arrangements on satisfactory terms, or at all. Our failure to secure these arrangements as needed could have a material adverse effect on our ability to complete the development of our product candidates or, to commercialize them, if approved. We may be unable to conclude agreements for commercial supply with third-party manufacturers or may be unable to do so on acceptable terms. There may be difficulties in scaling up to commercial quantities and formulation of our product candidates, and the costs of manufacturing could be prohibitive.

Further, the FDA, EMA and other foreign regulatory authorities require that our product candidates be manufactured according to cGMP and similar foreign standards. Pharmaceutical manufacturers and their subcontractors are required to register their facilities and/or products manufactured at the time of submission of the marketing application and then annually thereafter with the FDA, EMA and other foreign regulatory agencies. They are also subject to pre-approval inspections and periodic unannounced inspections by the FDA, EMA and other foreign regulatory agencies. Any subsequent discovery of problems with a product, or a manufacturing or laboratory facility used by us or our collaborators, may result in restrictions on the product or on the manufacturing or laboratory facility, including product recall, suspension of manufacturing, importation bans, product seizure or a voluntary withdrawal of the drug from the market. Any failure by our, or our collaborators', third-party manufacturers to comply with cGMP or any failure to deliver sufficient quantities of product candidates in a timely manner, could lead to a delay in, or failure to obtain, regulatory approval of any of our product candidates.

In addition to third-party manufacturers, we rely on other third parties to store, monitor, label, package and transport bulk drug substance and drug product. If we are unable to arrange for such third-party sources, or fail to do so on commercially reasonable terms, we may not be able to successfully supply sufficient product candidate or we may be delayed in doing so. Such failure or substantial delay could materially harm our business.

If any third-party manufacturer of our product candidates is unable to increase the scale of its production of our product candidates, and/or increase the product yield of its manufacturing, then our costs to manufacture the product may increase and commercialization may be delayed.

In order to produce sufficient quantities to meet the demand for clinical trials and, if approved, subsequent commercialization of our product candidates, our third-party manufacturers will be required to increase their production and optimize their manufacturing processes while maintaining the quality of the product. The transition to larger scale production could prove difficult. In addition, if our third-party manufacturers are not able to optimize their manufacturing processes to increase the product yield for our product candidates, or if they are unable to produce increased amounts of our product candidates while maintaining the quality of the product, then we may not be able to meet the requirements for registration and validation and the demands of clinical trials or market demands, which could delay regulatory approvals and decrease our ability to generate profits and have a material adverse impact on our business and results of operation.

We rely on third parties to conduct our pre-clinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties, including to comply with applicable laws and regulations or meet expected deadlines, our business could be substantially harmed.

We rely on entities outside of our control, which may include academic institutions, CROs, hospitals, clinics and other third-party collaborators, to monitor, support, conduct and/or oversee pre-clinical and clinical studies of our current and future product candidates. As a result, we have less control over the timing and cost of these studies and the ability to recruit trial subjects than if we conducted these trials with our own personnel. For example, an investigator-sponsored Phase 2 proof-of-concept clinical trial examining XEN1101 in MDD and anhedonia is being conducted in partnership with academic collaborators at the Icahn School of Medicine at Mount Sinai.

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

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

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

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

Switching or adding CROs, CMOs or other suppliers can involve substantial cost and require extensive management time and focus. In addition, there is a natural transition period when a new CRO, CMO or supplier commences work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. If we are required to seek alternative supply arrangements, the resulting delays and potential inability to find a suitable replacement could materially and adversely impact our business.

Risks Related to Intellectual Property

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

Our commercial success will depend, in part, on our ability to obtain and maintain patent, trademark and trade secret protection of our product candidates and future products, their respective components, formulations, methods used to manufacture them and methods of treatment, as well as successfully defending against third-party challenges. We evaluate our global patent portfolio in the ordinary course of business to enhance patent protection in areas of our strategic focus and in key markets for our product candidates and future products and may abandon existing patents or patent applications related to terminated development programs, areas, or markets of low strategic importance. Patents might not issue with respect to our patent applications that are currently pending, and issued patents might later be found to be invalid or unenforceable, be interpreted in a manner that does not adequately protect our product candidates or any future products, or fail to otherwise provide us with any competitive advantage. The patent position of biotechnology and pharmaceutical companies is generally highly uncertain because it involves complex legal and factual considerations that may be impacted by changes in the law. In addition, the standards applied by the U.S. Patent and Trademark Office, or USPTO, and foreign patent offices in issuing patents are not always applied uniformly or predictably, and also may be subject to changing law. Consequently, patents may not issue from our pending patent applications, or we may end up with patent claims of different scope in different jurisdictions. As such, we do not know the degree of future protection that we will have on our future products and proprietary technology, if any, and a failure to obtain adequate intellectual property protection with respect to our product candidates and future products, as well as other proprietary technology could have a material adverse impact on our business and ability to achieve profitability.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or patent applications will be due to be paid to the USPTO and various governmental patent offices outside of the U.S. in several stages over the lifetime of the patents and/or applications. The USPTO and foreign governmental patent offices require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application and maintenance process. We employ reputable law firms and other professionals to help us comply with respect to the patents and patent applications that we own or co-own, and we rely upon collaborators to effect compliance with respect to the patents and patent applications that we out-license.

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

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

- others may be able to make compounds that are similar to our product candidates or future products but that are not covered by the claims of the patents that we own, co-own or may in-license;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- patents that we own, co-own or may in-license may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- we may obtain patents for certain compounds many years before we obtain marketing approval for products containing such compounds, and because patents have a limited life, the term(s) may begin to run out prior to the commercial sale of the related product, the commercial value of our patents may be limited;
- we might not have been the first to make or file upon the inventions covered by the patents or pending patent applications;
- it is possible that our pending patent applications will not issue as patents;
- we cannot predict the scope of protection of any patent issuing from our patent applications, including whether the patent applications that we own will result in patents with claims directed to our product candidates or future products or uses thereof in the United States or in foreign countries;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may fail to develop additional proprietary technologies that are patentable and/or may fail to adequately protect such technologies;
- the laws of certain foreign countries may not protect our intellectual property rights to the same extent as the laws of the U.S., or we may fail to apply for or obtain adequate intellectual property protection in all the jurisdictions in which we operate; and
- the patents of others may have an adverse effect on our business, for example by preventing us from commercializing our future products.

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

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

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

Many companies have encountered significant problems in protecting, enforcing and defending intellectual property rights in certain foreign countries. The legal systems of some countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property rights, particularly those relating to biotechnology and pharmaceutical products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally.

Proceedings to enforce our patent rights in foreign countries could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing as patents and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from our intellectual property.

We may be involved in lawsuits to enforce our patents or the patents of our licensors, which could be expensive, time consuming and unsuccessful, and those patents could be found invalid or unenforceable if challenged.

Any of our intellectual property rights could be challenged or invalidated despite measures we or our licensors take to obtain patent and other intellectual property protection with respect to our product candidates and proprietary technology.

Competitors may infringe our patents or the patents of our licensors. To stop infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent in suit is not valid or is not enforceable. In such case third parties may be able to use our technology without paying licensing fees or royalties. Even if the validity of our patents is upheld, a court may refuse to stop the other party from using the technology at issue on the ground that the other party's activities are not covered by our patents. In addition, third parties may affirmatively challenge our rights to, or the scope or validity of, our patents. An adverse result in any litigation or post-grant proceedings could put additional patents at risk of being invalidated, held unenforceable or interpreted narrowly, and could put any of our patent applications at risk of not yielding an issued patent. Any efforts to enforce our intellectual property rights are likely to be costly and may divert the efforts of our scientific and management personnel.

For example, if we were to initiate legal proceedings against a third-party to enforce a patent covering one of our product candidates or future products, the defendant could defend or counterclaim that our patent is invalid and/or unenforceable. In patent litigation in the U.S. and in some foreign countries, defendant defenses and counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness, patent ineligibility, loss of priority claims, lack of written description, or lack of enablement. Grounds for an assertion of unenforceability could be an allegation that someone connected with prosecution of the patent withheld material information from the USPTO or an applicable foreign counterpart where such a duty to disclose exists, or made a misleading statement, during prosecution. For example, administrative proceedings such as derivation proceedings, entitlement proceedings, ex parte reexamination, inter partes review, postgrant review, or opposition proceedings, provoked by third parties or initiated by the USPTO or any foreign patent authority may be used to challenge inventorship, ownership, claim scope, or validity of our patents or a patent of our licensor. An unfavorable outcome in any of these proceedings could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms, if any license is offered at all. Litigation or administrative proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees.

With respect to challenges to the validity of our patents or the patents of our licensors, for example, there might be prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on a product candidate or future product. As another example, a litigant or the USPTO itself could challenge our patents on this basis even if we believe that we have conducted our patent prosecution in accordance with the duty of candor and in good faith. The outcome following such challenges is unpredictable. Even if a challenger does not prevail, our patent claims may be construed in a manner that would limit our ability to enforce such claims against the challenger and others. The cost of defending such a challenge, particularly in a foreign country, and any resulting loss of patent protection could have a material adverse impact on one or more of our product candidates and our business.

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

There have been and may be times in the future when certain patents that relate to our product candidates or any future products are controlled by our collaborators, including licensees, sublicensees or licensors. Although we may, under such arrangements, have rights to consult with our collaborators on actions taken as well as back-up rights of prosecution and enforcement, we have in the past and may in the future relinquish rights to prosecute and maintain patents and patent applications within our portfolio as well as the ability to assert such patents against infringers. For example, currently the rights relating to the patent portfolio for XEN901 (now known as NBI-921352), other selective Nav1.6 inhibitors and dual Nav1.2/1.6 inhibitors are exclusively licensed to Neurocrine Biosciences, and Neurocrine Biosciences has the first right to bring and control any action in connection with product infringement.

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

Claims that our product candidates or the sale, offer for sale, importation, manufacture, or use of our future products infringe the patent or other intellectual property rights of third parties could result in costly litigation, could require substantial time and money to resolve, even if litigation is avoided, and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, upon our ability to develop product candidates and commercialize our future products, without infringing the intellectual property rights or other proprietary rights of others. Third parties might allege that we, or our collaborators, are infringing, misappropriating, or otherwise violating their intellectual property rights. Such third parties might resort to litigation against us or other parties we have agreed to indemnify, which litigation could be based on either existing intellectual property or intellectual property that arises in the future.

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

The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, our future products, or methods of use either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity may be difficult. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on our business and operations. Furthermore, we may not have sufficient resources to bring these actions to a successful conclusion.

We may choose to challenge the enforceability or validity of claims of a third party's patent by requesting an administrative proceedings, for example, derivation proceedings, entitlement proceedings, ex parte reexamination, inter partes review, postgrant review, or opposition proceedings, before the USPTO or any foreign patent authority. These administrative proceedings are expensive and may consume our time or other resources. The costs of these administrative proceedings could be substantial and may consume our time or other resources. If we fail to obtain a favorable result in the USPTO, EPO or other foreign patent office then we may be exposed to litigation by a third party alleging that the patent may be infringed by our product candidates or future products.

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

Third parties may be able to sustain the costs of complex intellectual property litigation or proceedings more effectively than we can. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to conduct our clinical trials, continue our internal research programs, in-license needed technology, or enter into strategic collaborations that would help us bring our product candidates to market.

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

Any future intellectual property litigation other administrative proceedings will result in additional expense and distraction of our personnel. There is inevitable uncertainty in intellectual property litigation, and we could lose, even if the case against us is weak or flawed. An unfavorable outcome in such litigation or proceedings may expose us or any future strategic collaborators to loss of our proprietary position, expose us to significant liabilities, or require us to seek licenses that may not be available on commercially acceptable terms, if at all, each of which could have a material adverse effect on our business. If we are found to infringe a third-party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or future product. Alternatively, we may be required to obtain a license from such third-party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or future product.

For example, if third parties successfully assert their intellectual property rights against us, we might be barred from using certain aspects of our technology or barred from developing and commercializing certain future products. Alternatively, we may be required to pay substantial damage awards to the plaintiff, including up to treble damages and attorneys' fees if we are found to have willfully infringed a patent. As another alternative, we may be required to obtain a license from the intellectual property owner to continue our research and development programs or to market any resulting product. It is also possible that we may be required to modify or redesign our product candidates or future products, if any, in order to avoid infringing or otherwise violating third-party intellectual property rights. This may not be technically or commercially feasible, may render those products less competitive, or may delay or prevent the entry of those products to the market. Any of the foregoing could limit our research and development activities, our ability to commercialize one or more product candidates, or both.

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

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

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

Under existing or future license and other agreements, we are or may become subject to various obligations, including diligence obligations such as development and commercialization obligations, as well as potential milestone payments and other obligations. If we fail to comply with any of these obligations or otherwise breach our license agreements, our licensing partners may have the right to terminate the applicable license in whole or in part or convert an exclusive license to a non-exclusive license. Generally, the loss of any such license, or any license exclusivity thereunder, could materially harm our business, prospects, financial condition and results of operations.

If we are unable to prevent unauthorized disclosure of trade secrets and other proprietary information, our competitive position could be harmed.

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

In addition, we, or our licensors, may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patents, trade secrets, or other intellectual property as an inventor or co-inventor. For example, we, or our licensors, may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or our, or our licensors', ownership of our owned or in-licensed patents, trade secrets or other intellectual property. If we, or our licensors, fail in defending against any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

Changes in U.S. patent law, or laws in other countries, could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our patents, thereby impairing our ability to protect our product candidates and future products.

Our success is heavily dependent on intellectual property, particularly patents. The patent positions of pharmaceutical and biopharmaceutical companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in patents in these fields has emerged to date in the U.S. or other countries. In addition, Congress or other foreign legislative bodies may pass patent reform legislation that is unfavorable to us. For example, there have been recent changes regarding how patent laws are interpreted, and both the USPTO and Congress have recently made significant changes to the patent system. There have been U.S. Supreme Court decisions that now show a trend of the Supreme Court which is distinctly negative on some patents. The trend of these decisions along with resulting changes in patentability requirements being implemented by the USPTO could make it increasingly difficult for us to obtain, maintain and/or enforce patents on our products. We cannot accurately predict future changes in the interpretation of patent laws or changes to patent laws which might be enacted into law. Those changes may materially affect our patents, our ability to obtain patents, the costs to prosecute our patent applications and enforce our patents and/or the patents and applications of our collaborators. The patent situation in these fields outside the U.S. also has uncertainties. Changes in either the patent laws or in interpretations of patent laws in the U.S. and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in the patents we own or to which we have a license or third-party patents. As an example, European patent applications have the option, upon issuance of a patent, of becoming a Unitary Patent, which is subject to the jurisdiction of the Unitary Patent Court, or UPC. The option of a Unitary Patent and the creation of the UPC are significant changes in European patent practice. As the UPC is a new court system, there is little precedent for the court, increasing the uncertainty of any litigation in the UPC.

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

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

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

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, if any, one or more U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Act. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than five years, or even less than we request if that number is less than five years.

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

If our trademarks are not adequately protected, we may not be able to build name recognition in our markets of interest, which could adversely affect our business.

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

Moreover, any name we have proposed to use with our product candidates in the United States, regardless of whether we have registered it or applied to register it as a trademark, must be approved by the FDA. Similar requirements exist in Europe and other foreign countries. If the FDA (or an equivalent administrative body in a foreign country) objects to any of our proposed product names, we may need to identify a suitable substitute name, for example, that would qualify under applicable trademark laws, not infringe the existing rights of third parties, and be acceptable to the FDA. This may require additional expense.

In addition, there could be potential trademark infringement claims brought by owners of other registered trademarks that incorporate variations of our registered or unregistered trademarks. If we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks. If we are unable to establish name recognition based on our trademarks, we may not be able to compete effectively, and our business may be adversely affected.

Risks Related to Ownership of Our Common Shares

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

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

- announcements by us or our competitors of new products, product candidates or new uses for existing products, significant contracts, commercial relationships or capital commitments and the timing of these introductions or announcements;

- actions by any of our collaborators regarding our product candidates they are developing, including announcements regarding clinical or regulatory decisions or developments of our collaboration;
- unanticipated serious safety concerns related to the use of any of our products and product candidates;
- negative or inconclusive results from clinical trials of our product candidates, leading to a decision or requirement to conduct additional pre-clinical testing or clinical trials or resulting in a decision to terminate the continued development of a product candidate;
- delays of clinical trials of our product candidates;
- failure to obtain or delays in obtaining or maintaining product approvals or clearances from regulatory authorities;
- adverse regulatory or reimbursement announcements;
- announcements by us or our competitors of significant acquisitions, strategic collaborations, licenses, joint ventures or capital commitments;
- the results of our efforts to discover or develop additional product candidates;
- our dependence on third parties, including our collaborators, CROs, clinical trial sponsors and clinical investigators;
- regulatory or legal developments in Canada, the U.S. or other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- actual or anticipated quarterly variations in our financial results or those of our competitors;
- sales of common shares by us, our insiders or our shareholders in the future, as well as the overall trading volume of our common shares;
- changes in the structure of healthcare payment systems;
- commencement of, or our involvement in, litigation;
- the impact of pandemics, epidemics or other public health crises on our business and the macroeconomic environment;
- general economic, industry and market conditions;
- market conditions in the pharmaceutical and biotechnology sectors and other factors that may be unrelated to our operating performance or the operating performance of our competitors, including changes in market valuations of similar companies; and
- the other factors described in this “Risk Factors” section.

In addition, the stock market in general, and Nasdaq and the biopharmaceutical industry in particular, have from time to time experienced volatility that often has been unrelated to the operating performance of the underlying companies. The COVID-19 pandemic and rising inflation and interest rates, for example, resulted in significant volatility. These broad market and industry fluctuations may adversely affect the market price of our common shares, regardless of our operating performance. In several recent situations where the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our shareholders were to bring a lawsuit against us, the defense and disposition of the lawsuit could be costly and divert the time and attention of our management and harm our operating results.

Future sales and issuances of our common shares or securities convertible into or exchangeable for common shares would cause our shareholders to incur dilution and could cause the market price of our common shares to fall.

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

Pursuant to our equity incentive plans, our compensation committee (or a subset or delegate thereof) is authorized to grant equity-based incentive awards to our employees, directors and consultants. Future stock option grants and issuances of common shares under our share-based compensation plans will result in dilution to all shareholders and may have an adverse effect on the market price of our common shares.

In addition, in the future, we may issue additional common shares, preferred shares, or other equity or debt securities convertible into common shares in connection with a financing, collaboration agreement, acquisition, litigation settlement, employee arrangements or otherwise. We may also issue additional common shares upon the exercise of pre-funded warrants that we have issued from time to time. Any such issuance, including any issuances pursuant to our "at-the-market" equity offering program under our sales agreement with Jefferies and Stifel, could result in substantial dilution to our existing shareholders and could cause the market price of our common shares to decline.

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

We are governed by the Canada Business Corporations Act, or CBCA, and other relevant laws, which may affect the rights of shareholders differently than those of a company governed by the laws of a U.S. jurisdiction, and may, together with our articles and by-laws, have the effect of delaying, deferring or discouraging another party from acquiring control of our company by means of a tender offer, a proxy contest or otherwise, or may affect the price an acquiring party would be willing to offer in such an instance. The material differences between the CBCA and Delaware General Corporation Law, or DGCL, that may have the greatest such effect include, but are not limited to, the following: (i) for material corporate transactions (such as mergers and amalgamations, other extraordinary corporate transactions or amendments to our articles) the CBCA generally requires a two-thirds majority vote by shareholders, whereas DGCL generally only requires a majority vote; and (ii) under the CBCA, holders of 5% or more of our shares that carry the right to vote at a meeting of shareholders can requisition a special meeting of shareholders, whereas such right does not exist under the DGCL. In addition, our board of directors is responsible for appointing the members of our management team and certain provisions of the CBCA and our articles and by-laws may frustrate or prevent any attempts by our shareholders to replace or remove our current management by making it more difficult for shareholders to replace members of our board of directors. Certain of these provisions include the following:

- shareholders cannot amend our articles unless such amendment is approved by shareholders holding at least two-thirds of the shares entitled to vote on such approval;
- shareholders must give advance notice to nominate directors or to submit proposals for consideration at shareholders' meetings; and
- applicable Canadian corporate and securities laws generally require, subject to certain exceptions, a tender offer (also known as a take-over bid) to remain open for a minimum of 105 days and that more than 50% of the outstanding securities not owned by the offeror be tendered before the offeror may take up the securities.

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

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

We are governed by the CBCA and our principal place of business is in British Columbia, Canada. Many of our directors and officers reside outside of the U.S., and all or a substantial portion of their assets as well as all or a substantial portion of our assets are located outside the U.S. As a result, it may be difficult for investors to effect service of process within the U.S. upon us and certain of our directors and officers or to enforce judgments obtained against us or such persons, in U.S. courts, in any action, including actions predicated upon the civil liability provisions of U.S. federal securities laws or any other laws of the U.S. Additionally, rights predicated solely upon civil liability provisions of U.S. federal securities laws or any other laws of the U.S. may not be enforceable in original actions, or actions to enforce judgments obtained in U.S. courts, brought in Canadian courts, including courts in the Province of British Columbia.

We are at risk of securities class action litigation.

Securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology companies have experienced significant share price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business. In addition, an increase in litigation against biotechnology companies may make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage.

Our management has broad discretion over the use of our cash and we may not use our cash effectively, which could adversely affect our results of operations.

Our management has broad discretion in the application of our cash resources. Shareholders may not agree with our decisions, and our use of our cash resources may not improve our results of operation or enhance the value of our common shares. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates and cause the market price of our common shares to decline. In addition, pending their use, they may be placed in investments that do not produce significant income or that may lose value.

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

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

Reports published by analysts, including projections in those reports that differ from our actual results, could adversely affect the price and trading volume of our common shares.

The trading market for our common shares depends in part on the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us issues an adverse opinion about our company, our common share price would likely decline. If one or more of these analysts ceases research coverage of us or fails to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause the price of our common shares or trading volume to decline.

There is no public market for our outstanding pre-funded warrants.

There is no public trading market for our outstanding pre-funded warrants and we do not expect a market to develop. In addition, we do not intend to list the outstanding pre-funded warrants on Nasdaq or any other national securities exchange or nationally recognized trading system. Without an active trading market, the liquidity of the outstanding pre-funded warrants will be limited.

General Risk Factors

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

Global credit and financial markets have at times experienced extreme disruptions, including in connection with the COVID-19 pandemic, characterized by increased market volatility, increased rates of inflation, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. Similarly, the current conflicts between Ukraine and Russia and in the Middle East, as well as recent failures in the global banking sector, have created volatility in the capital markets and are expected to have further global economic consequences. Limited liquidity, defaults, non-performance and other adverse developments affecting financial institutions or parties with which we do business, or perceptions regarding these or similar risks, have in the past and may in the future lead to market-wide liquidity problems. For example, in March 2023, Silicon Valley Bank was closed and placed into receivership and, subsequently, additional financial institutions have been placed into receivership. There is no guarantee that the U.S. government or governments in other jurisdictions will intervene to provide access to uninsured funds in the future in the event of the failure of other financial institutions, or that the U.S. government or governments in other jurisdictions would do so in a timely fashion. 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, including as a result of a pandemic, political unrest or war, or further instability of the global banking sector, it may make any necessary equity or debt 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 and could require us to delay or abandon development or commercialization plans. In addition, there is a risk that one or more of our current collaborators, service providers, manufacturers and other partners would not survive or be able to meet their commitments to us under such circumstances, which could directly affect our ability to attain our operating goals on schedule and on budget.

We have incurred, and expect to continue to incur, significant costs as a result of laws, regulations and investor-driven standards relating to corporate governance and other matters.

Laws and regulations affecting public companies, including provisions of the Dodd-Frank Wall Street Reform and Consumer Protection Act, Sarbanes-Oxley Act of 2002, the CBCA, applicable Canadian securities laws, and rules adopted or proposed by the SEC, Nasdaq, Corporations Canada and applicable Canadian securities regulators have resulted in, and will continue to result in, significant compliance costs to us as we evaluate the implications of these rules and respond to their requirements.

Compliance with the various reporting and other requirements applicable to public companies also requires considerable time and attention of management. In the future, if we are not able to issue an evaluation of our internal control over financial reporting, as required, or we or our independent registered public accounting firm determine that our internal control over financial reporting is not effective, this shortcoming could have an adverse effect on our business and financial results and the price of our common shares could be negatively affected. New rules could make it more difficult or more costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the coverage that is the same or similar to our current coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors and board committees, and as our executive officers. We cannot predict or estimate the total amount of the costs we may incur or the timing of such costs to comply with these rules and regulations.

In addition, the SEC and applicable Canadian securities regulators regularly pursue various rulemaking efforts, including recently with respect to environmental, social and governance, or ESG, matters. A variety of organizations also measure the performance of companies on such ESG topics, and the results of these assessments are widely publicized. Investment in funds that specialize in companies that perform well in such assessments are increasingly popular, and major institutional investors have publicly emphasized the importance of such ESG measures to their investment decisions. If additional rules regarding ESG matters are adopted or if investors continue to increase their focus on ESG matters, we could incur substantially higher costs in our efforts to comply and cannot be certain that our efforts will be viewed as adequate by regulators or by such investors.

Item 1B. Unresolved Staff Comments

None.

Item 1C. Cybersecurity

We rely on both internal information technology systems and networks, and those of third-party vendors and contractors, to acquire, transmit, store and otherwise process information in connection with our business activities. Our ability to effectively manage our business depends on the security, reliability and adequacy of our and our third-party contractors' and vendors' technology systems. As such, we have implemented an information security program designed to assess, identify, and manage risks from cybersecurity threats.

We perform risk assessments relating to cybersecurity and technology risks at least annually. Our cybersecurity risk management program has been developed based on industry standards, including those published by the National Institute of Standards and Technology ("NIST"). Highlights of the program include:

- Corporate policies and procedures that guide our use of information systems, confidentiality and security strategy;
- Identifying critical assets and high-risk threats, and implementing technical prevention and detection controls and response and recovery practices;
- A third-party risk management process to assist in making risk-informed technology product and services decisions on third parties who provide, manage, store or have access to material data or information, including the completion of security questionnaires and independent assessments of controls, audits and/or contract terms;
- Defined data loss prevention standards in place to detect and prevent data loss, including requiring third-party service providers with access to personal, confidential or proprietary information to implement and maintain comprehensive cybersecurity practices consistent with applicable legal standards and industry best practices;
- Security awareness training for employees to identify cybersecurity concerns and take appropriate actions; and
- Evaluating our program's effectiveness by performing regular internal and third-party assessments of our controls, including external penetration testing and consultation on security enhancements.

Risks identified through our cybersecurity program are assessed to determine the potential impact and likelihood of occurrence and mitigation plans are developed and implemented accordingly.

The Audit Committee of our Board of Directors bears the primary responsibility for oversight of cybersecurity risks. The Audit Committee is composed of board members with diverse expertise, including risk management, technology and finance, equipping them to oversee cybersecurity risks effectively. Management's oversight is performed through an IT Steering Committee, a subset of executive management including our Chief Financial Officer, or CFO, and Chief Legal Officer, and relevant functional expertise, including our Senior Vice President, Information Systems, or SVP, IS. Our SVP, IS, is the primary member of the IT Steering Committee charged with responsibility for assessing, monitoring and managing our cybersecurity risks. With over 20 years of experience in information technology strategy and operations, his background includes extensive experience as an IT executive at various companies. At least annually, the SVP, IS, and the CFO provide a comprehensive report to the Audit Committee regarding cybersecurity risk assessments, emerging threats and changes to industry standards, and incident reports and remediation, if any.

The SVP, IS, oversees processes for the regular monitoring of our information systems, including potential vulnerabilities. In the event of a cybersecurity incident, the IT organization and designated members of executive management follow an established Cybersecurity Incident Response Plan. This plan includes immediate actions to contain the threat, mitigate the impact and assess materiality, and requires retrospective review and identification of corrective actions to reduce future risk.

During the fiscal year ended December 31, 2023, we did not experience any material impact to our business, financial position or operations resulting from previously identified cyberattacks or other information security incidents, but we cannot provide assurance that they will not be materially affected in the future by such risks or any future material breaches. For a discussion of these risks, see "Item 1A—Risk Factors—Risk Related to Our Business and Industry—Our business and operations could suffer in the event of an actual or perceived information security incident such as a cybersecurity breach, system failure, or other compromise of our systems and/or information, including information held by a third-party contractor or vendor."

Item 2. Properties

Our headquarters are located in Burnaby, British Columbia, where we currently occupy approximately 53,023 square feet of office and laboratory space. The term of the lease expires in June 2032. We currently pay an aggregate of approximately $145,353 per month in base rent, property tax, common area maintenance fees and management fees, and the landlord holds a security deposit equal to approximately $67,932.

We also occupy approximately 17,057 square feet of office space in Needham, Massachusetts. The term of the lease expires in November 2027. We currently pay an aggregate of approximately $63,964 per month in base rent and the landlord holds a security deposit equal to approximately $187,627.

We believe that our existing facilities are adequate to meet our business requirements for the near-term and that additional space will be available on commercially reasonable terms, if required.

Item 3. Legal Proceedings

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

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common shares have been traded on the Nasdaq Global Market since November 5, 2014 under the symbol "XENE." On February 26, 2024, the last reported sale price of our common shares was $49.13 per share.

Holders

As of February 26, 2024, there were approximately 82 holders of record of our common shares. The actual number of shareholders is greater than this number of record holders and includes shareholders who are beneficial owners but whose common shares are held in street name by brokers and other nominees.

Dividends

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

Canadian withholding tax at a rate of 25% (subject to reduction under the provisions of any applicable income tax treaty or convention to which Canada is a signatory) will be payable on the gross amount of a dividend on our common shares paid or credited, or deemed to be paid or credited, to a holder of our common shares who, for purposes of the Income Tax Act (Canada), is not (and is not deemed to be) resident in Canada, or a Non-Resident of Canada Holder. The Canadian withholding tax will be deducted directly by us or our paying agent from the amount of the dividend otherwise payable and remitted to the Receiver General for Canada. The rate of withholding tax applicable to a dividend paid on our common shares to a Non-Resident of Canada Holder who is a resident of the U.S. for purposes of the Canada-U.S. Tax Convention (1980), or the Convention, is the beneficial owner of the dividend and qualifies for the full benefits of the Convention will generally be reduced to 15% or, if such a Non-Resident of Canada Holder is a company beneficially owning at least 10% of our voting shares, to 5%. Not all persons who are residents of the U.S. for purposes of the Convention will qualify for the benefits of the Convention. In some circumstances, persons deriving amounts through fiscally transparent entities (including limited liability companies) may not be entitled to benefits under the Convention. The Multilateral Convention to Implement Tax Treaty Related Measures to Prevent Base Erosion and Profit Shifting, of which Canada is a signatory, affects many of Canada's tax treaties (but not the Convention), including the ability to claim benefits thereunder. Non-Resident of Canada Holders should consult their own tax advisors to determine their entitlement to relief under an applicable income tax treaty or convention.

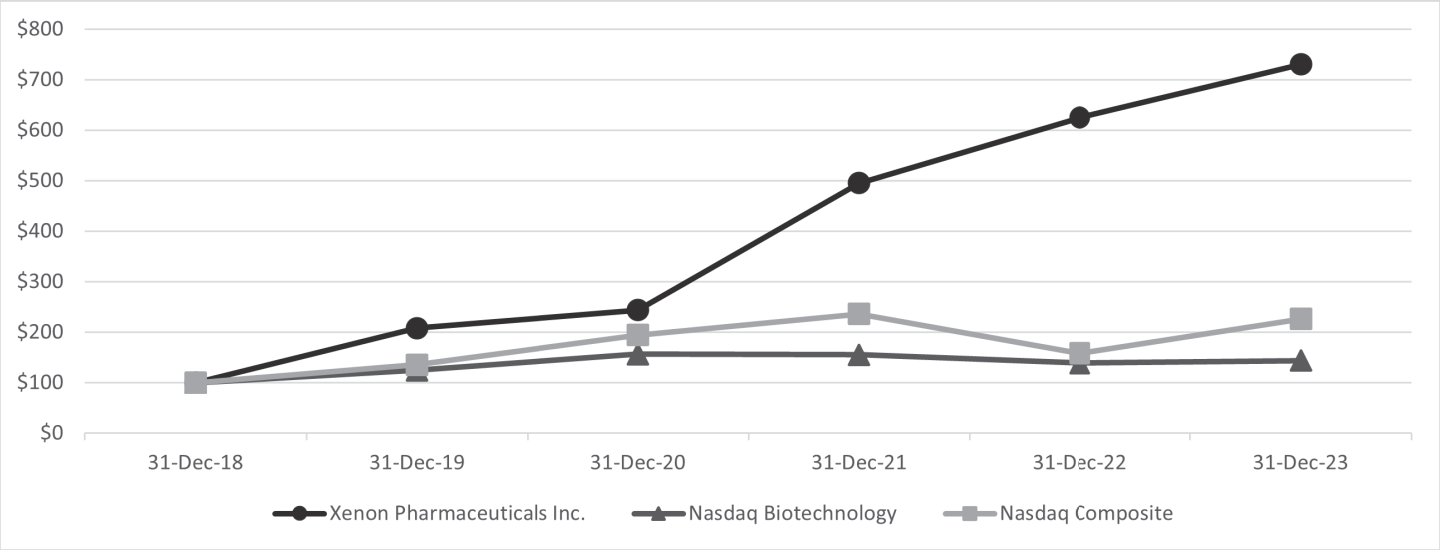
Securities Authorized for Issuance Under Equity Compensation Plans

The information required by this item is incorporated by reference to our Proxy Statement for the 2024 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2023.

Stock Performance Graph

This performance graph shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or incorporated by reference into any filing of Xenon Pharmaceuticals Inc. under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

The following graph shows a comparison of the total cumulative returns of an investment of $100 in cash from December 31, 2018 through December 31, 2023 in (i) our common shares, (ii) the Nasdaq Biotechnology Index, and (iii) the Nasdaq Composite Index. The comparisons in the graph are required by the SEC and are not intended to forecast or be indicative of the possible future performance of our common stock. The graph assumes that all dividends have been reinvested (to date, we have not declared any dividends).



Issuer Repurchases of Equity Securities

None.

Item 6. [Reserved]

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

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

Overview

We are a neuroscience-focused biopharmaceutical company committed to discovering, developing, and commercializing innovative therapeutics to improve the lives of people living with neurological and psychiatric disorders. We are advancing a novel product pipeline to address areas of high unmet medical need, including epilepsy and depression.

XEN1101

XEN1101 is a novel, potent Kv7 potassium channel opener being developed for the treatment of epilepsy, major depressive disorder, or MDD, and potentially other neurological disorders.

XEN1101 for Epilepsy (Focal Onset Seizures)

Our XEN1101 Phase 3 epilepsy program includes two identical Phase 3 clinical trials, called X-TOLE2 and X-TOLE3, which are designed closely after the Phase 2b X-TOLE clinical trial. These multicenter, randomized, double-blind, placebo-controlled trials are evaluating the clinical efficacy, safety, and tolerability of 15 mg or 25 mg of XEN1101 administered once-daily with food as adjunctive treatment in approximately 360 patients per study with focal onset seizures, or FOS. The primary efficacy endpoint is the median percent change, or MPC, in monthly seizure frequency from baseline through the double-blind period, or DBP, of XEN1101 compared to placebo. We anticipate patient enrollment in X-TOLE2 will be completed in late 2024 to early 2025.

XEN1101 for Epilepsy (Primary Generalized Tonic-Clonic Seizures)

Our Phase 3 X-ACKT clinical trial is intended to support potential regulatory submissions in an additional epilepsy indication of primary generalized tonic-clonic seizures, or PGTCS. This multicenter, randomized, double-blind, placebo-controlled study is evaluating the clinical efficacy, safety, and tolerability of 25 mg of XEN1101 administered once-daily with food as adjunctive treatment in approximately 160 patients with PGTCS. The primary efficacy endpoint is the MPC in monthly PGTCS frequency from baseline through the DBP of XEN1101 compared to placebo.

XEN1101 for Epilepsy (Open-Label Extension)

Upon completion of the DBP in X-TOLE2, X-TOLE3, or X-ACKT, eligible patients may enter an open-label extension, or OLE, study for up to three years. In addition, the ongoing X-TOLE Phase 2b OLE has been extended from five to seven years and continues to generate important long-term data for XEN1101.

XEN1101 for Major Depressive Disorder

In November 2023, we reported promising topline results from the Phase 2 proof-of-concept X-NOVA clinical trial, which evaluated the clinical efficacy, safety, and tolerability of 10 mg and 20 mg of XEN1101 administered once-daily with food in 168 patients with moderate to severe MDD. The primary endpoint of the study was a change in the Montgomery-Åsberg Depression Rating Scale, or MADRS, at week 6. A clear dose response and a clinically meaningful, but not statistically significant, 3.04 difference between placebo and the XEN1101 20 mg group (p=0.135) was observed. Statistical significance was achieved on other secondary efficacy endpoints, including the Hamilton Depression Rating Scale, or HAM-D17; the Snaith-Hamilton Pleasure Scale, or SHAPS, measuring anhedonia; and MADRS at week 1, demonstrating early onset of efficacy. XEN1101 was generally well tolerated with similar rates of overall adverse events, as well as similar rates of discontinuation, reported across all treatment arms. No serious adverse events were reported in the two XEN1101 treatment groups, XEN1101 was not associated with notable weight gain and participants did not report any notable sexual dysfunction. We are actively planning for late-stage clinical development of XEN1101 in MDD and expect to initiate the Phase 3 clinical program in 2024. We are also evaluating other potential indications for the future development of XEN1101.

In addition, we are collaborating with the Icahn School of Medicine at Mount Sinai to support an ongoing investigator-sponsored Phase 2 proof-of-concept, randomized, parallel-arm, placebo-controlled multi-site study of XEN1101 for the treatment of MDD in approximately 60 subjects. See "Recent Developments" for additional information about topline X-NOVA results.

Other Pipeline Opportunities

We continue to leverage our extensive ion channel expertise and drug discovery capabilities to identify validated drug targets and develop new product candidates. The near-term focus is on internal development candidates targeting Kv7, Nav1.1 and Nav1.7.

Partnered Program: NBI-921352

We have an ongoing collaboration with Neurocrine Biosciences to develop treatments for epilepsy. Neurocrine Biosciences has an exclusive license to XEN901, now known as NBI-921352, a selective Nav1.6 sodium channel inhibitor. In November 2023, Neurocrine Biosciences reported that the Phase 2 clinical trial evaluating NBI-921352 in adult patients with FOS failed to demonstrate meaningful reduction in seizure frequency. Neurocrine Biosciences guided that no further development with NBI-921352 in FOS is planned at this time. A Phase 2 clinical trial is currently underway evaluating NBI-921352 in patients aged between 2 and 21 years with SCN8A developmental and epileptic encephalopathy.

We have funded our operations primarily through the sale of equity securities, including receiving net proceeds of approximately $324.0 million from the sale of common shares and pre-funded warrants in a public offering in November 2023, funding received from our licensees and collaborators, and debt financing. We did not recognize any revenue in the year ended December 31, 2023, as compared to revenue from collaboration agreements of $9.4 million and $18.4 million for the years ended December 31, 2022 and 2021, respectively. To date, we have not had any products approved for sale and have not generated any revenue from product sales. We do not expect to generate revenue from product sales unless and until we successfully complete development and obtain regulatory approval for a product candidate, which we expect will take a number of years, if ever, and the outcome of which is subject to significant uncertainty.

We will continue to require additional capital to develop our product candidates and fund operations for the foreseeable future. We have incurred net losses in each year since inception and expect to continue to incur net losses for the foreseeable future. Our net losses were $182.4 million, $125.4 million, and $78.9 million for the years ended December 31, 2023, 2022, and 2021, respectively. As of December 31, 2023, we had an accumulated deficit of $665.1 million. Substantially all of our net losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We anticipate that our operating expenses will increase substantially, particularly as we:

- continue our research and pre-clinical and clinical development of our product candidates;
- seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical trials;
- require the manufacture of larger quantities of our product candidates for clinical development and potential commercialization;
- attract, hire and retain skilled personnel;
- acquire or in-license other assets and technologies;
- maintain, protect and expand our intellectual property portfolio; and
- create additional infrastructure to support our operations and any future commercialization efforts.

Financial Operations Overview

Revenue

To date, our revenue has been primarily derived from collaboration and licensing agreements and we have not generated any revenue from product sales. If our development efforts for our product candidates are successful and result in regulatory approval, we may generate revenue in the future from product sales. We cannot predict if, when, or to what extent we will generate revenue from the commercialization and sale of our product candidates. We may never succeed in obtaining regulatory approval for any of our product candidates.

We may also generate revenue in the future from payments as a result of license or collaboration agreements for any of our product candidates or intellectual property, such as our license and collaboration agreement with Neurocrine Biosciences, or the Neurocrine Collaboration, described in “Business — Collaborations, Commercial and License Agreements” and “Note 11” of the consolidated financial statements included elsewhere in this Annual Report on Form 10-K. We cannot provide assurance as to the timing of future milestone or royalty payments under the Neurocrine Collaboration, or that we will receive any of these payments at all.

The following table is a summary of revenue recognized for the years ended December 31, 2023, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Neurocrine Biosciences:			
Recognition of the transaction price	$ —	$ 372	$ 3,715
Research and development services	—	1,938	6,452
Milestone payments	—	7,124	5,270
Pacira BioSciences:			
Milestone payments	—	—	3,000
Total revenue	$ —	$ 9,434	$ 18,437

Pursuant to the terms of the Neurocrine Collaboration, we received an upfront cash payment of $30.0 million and a $20.0 million equity investment in our common shares in December 2019. The overall transaction price of the arrangement was measured and allocated to certain performance obligations and revenue was recognized as those performance obligations were completed. In September 2021, based on the regulatory approval of a clinical trial application in Europe for NBI-921352 for focal-onset seizures in adults, we received an aggregate milestone payment of $10.0 million in the form of $4.5 million cash and a $5.5 million equity investment in our common shares. Further, in January 2022, based on the U.S. Food and Drug Administration's ("FDA") approval to expand the SCN8A-DEE study population to include subjects aged between 2 and 11 years, we received an aggregate milestone payment of $15.0 million in the form of $6.75 million cash and $8.25 million equity investment in our common shares. In each instance, the equity investment was measured at fair value on the date of issuance and the resulting premium with the cash payment, was recognized as revenue. Research and development services were recognized as revenue at fair market value as the services were rendered. The research collaboration was completed in June 2022.

In the year ended December 31, 2021, we recognized revenue of $3.0 million in connection with our agreement with Pacira BioSciences, Inc., or the Pacira Agreement, for the global rights to develop and commercialize PCRX301 which included a $1.0 million milestone for the clearance of an investigational new drug application by the FDA and a $2.0 million milestone for the initiation of a Phase 1b clinical trial. No revenue was recognized in the years ended December 31, 2023 and December 31, 2022 in connection with the Pacira Agreement. In November 2022, Pacira BioSciences made the strategic decision to no longer pursue the clinical development of PCRX-301.

Operating Expenses

The following table summarizes our operating expenses for the years ended December 31, 2023, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Research and development	$ 167,512	$ 105,767	$ 75,463
General and administrative	46,542	32,810	21,967
Total operating expenses	$ 214,054	$ 138,577	$ 97,430

Research and Development Expenses

Research and development expenses represent costs incurred to conduct development of our proprietary product candidates and our drug discovery efforts, including any acquired or in-licensed product candidates or technology, and costs to support our partnered product candidates.

Research and development expenses consist of costs incurred in performing research and development activities, including:

- personnel-related expenses, consisting of salaries, benefits and stock-based compensation for employees engaged in scientific research and development;
- third-party expenses incurred in connection with the pre-clinical and clinical development of our product candidates, including under agreements with CROs;
- third-party expenses relating to formulation, process development and manufacture of drug substance and drug product for use in our pre-clinical testing and clinical trials;
- third-party acquisition, license and collaboration fees;
- laboratory consumables; and
- certain indirect costs incurred in support of overall research and development activities, including facilities, depreciation and information technology costs.

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

We expense all research and development costs as incurred. Payments we make for research and development services prior to the services being rendered are recorded as prepaid assets in our consolidated balance sheets and are expensed as the services are provided. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and third-party service providers.

We expect that our research and development expenses will increase substantially in the future as we continue to invest in research and development activities related to developing our product candidates, including investments in manufacturing, as our programs advance into later stages of development and we continue to conduct clinical trials, advance our internal drug discovery programs into pre-clinical development and continue our early-stage research. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size, scope and duration of later-stage clinical trials.

Clinical development timelines, likelihood of regulatory approval, and commercialization and associated costs are uncertain, difficult to estimate, and can vary significantly. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming, and the successful development of our product candidates is highly uncertain. As a result, we cannot accurately estimate or know the nature, timing and costs that will be necessary to complete the pre-clinical and clinical development for any of our product candidates or when and to what extent we may generate revenue from the commercialization and sale of any of our product candidates or achieve profitability.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel-related expenses, consisting of salaries, benefits and stock-based compensation for our employees engaged in executive, finance, legal, business development, commercial and administrative functions, insurance costs, professional fees for auditing, tax and legal services, costs related to maintenance and filing of intellectual property, costs incurred as we prepare for commercialization, and allocated facility-related and information technology costs not otherwise included in research and development expenses.

We expect that general and administrative expenses will increase in the future as we expand our operating activities to support our continued research activities and development of our product candidates, and as we prepare for commercialization. We will also continue to incur increased accounting, audit, legal, regulatory, compliance and director and officer insurance costs as well as investor and public relations expenses associated with operating as a public company.

Other Income (Expense)

Interest income. Interest income consists of income earned on our cash and investment balances. We anticipate that our interest income will continue to fluctuate depending on our cash and investment balances and interest rates.

Unrealized fair value gain (loss) on trading securities. Trading securities are recorded at fair value. Unrealized fair value gain (loss) on trading securities is related to changes in market pricing on the investments during the period. We anticipate that unrealized fair value gain (loss) on trading securities will continue to fluctuate depending on our investment balance and market yields.

Foreign exchange gain (loss). Net foreign exchange gains and losses consisted of gains and losses from the impact of foreign exchange fluctuations on our monetary assets and liabilities that are denominated in currencies other than the U.S. dollar (principally the Canadian dollar). We will continue to incur substantial expenses in Canadian dollars and will remain subject to risks associated with foreign currency fluctuations.

Critical Accounting Policies and Significant Judgments and Estimates

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

The significant accounting policies that we believe to be most critical in fully understanding and evaluating our historical and future performance are revenue recognition, research and development costs and stock-based compensation. For additional information, see "Note 3" of the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Revenue recognition:

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

Our primary sources of revenue are derived from non-refundable upfront payments, funding for research and development services, milestone payments, and royalties under license and collaboration agreements.

In contracts where we have more than one performance obligation to provide our customer with goods or services, each performance obligation is evaluated to determine whether it is distinct. The consideration under the contract is then allocated between the distinct performance obligations based on their respective relative standalone selling prices. The estimated standalone selling price of each deliverable reflects our best estimate of what the selling price would be if the deliverable was regularly sold on a standalone basis and is determined by reference to market rates for the good or service when sold to others or by using an adjusted market assessment approach if selling price on a standalone basis is not available. We generally recognize revenue from non-refundable upfront payments over the estimated term of the performance obligation or period in which the underlying benefit is transferred to the customer. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

The consideration allocated to each distinct performance obligation is recognized as revenue when control is transferred to our customer for the related goods or services. Consideration in exchange for research and development services performed by us on behalf of the licensee is recognized upon performance of such activities at rates consistent with prevailing market rates. Consideration associated with at-risk substantive performance milestones, including sales-based milestones, is recognized as revenue when we determine it is probable that a significant reversal of the cumulative revenue recognized will not occur. At the end of each subsequent reporting period, we re-evaluate the probability of achievement of such milestones, and if necessary, adjust our estimate of the overall transaction price. Sales-based royalties received in connection with licenses of intellectual property are subject to a specific exception in the revenue standards, whereby the consideration is not included in the transaction price and recognized in revenue until the customer's subsequent sales or usages occur.

Research and development costs:

Research and development costs is a critical accounting policy due to the magnitude of the costs and the requirement to estimate the proportionate performance of vendors to calculate third-party accrued and prepaid research and development expenses.

We accrue for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of pre-clinical studies and clinical trials, and manufacturing activities. Third-party service providers generally provide estimates of proportionate performance to allow us to determine an appropriate accrual. When determining the adequacy of an accrual, we analyze progress based on the level of services performed, progress of the studies, including the phase or completion of events, and contracted costs. Payments made to third parties under these arrangements in advance of the receipt of the related services are recorded as prepaid expenses until the services are rendered. Our historical prepaid and accrual estimates have not been materially different from the actual costs.

Stock-based compensation:

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

We grant stock options to employees, consultants, directors and officers pursuant to our stock option plans. Compensation expense is recorded using the fair value method. We calculate the fair value of stock options using the Black-Scholes option-pricing model which requires that certain assumptions, including the expected life of the option and expected volatility of the stock, be estimated at the time that the options are granted. The expected volatility is based on the historical volatility of our common shares calculated based on a period of time commensurate with the expected term assumption. The expected term of our stock options has been determined utilizing our available historical data and we recognize forfeitures as they occur. We amortize the fair value of stock options using the straight-line method over the vesting period of the options.

Results of Operations

Comparison of Years Ended December 31, 2023, 2022 and 2021

The following table summarizes the results of our operations for the years ended December 31, 2023, 2022 and 2021 together with changes in those items (in thousands):

	Year Ended December 31,			Change 2023 vs. 2022	Change 2022 vs. 2021
	2023	2022	2021	Increase/(Decrease)	Increase/(Decrease)
Revenue	$ —	$ 9,434	$ 18,437	$ (9,434)	$ (9,003)
Research and development expenses	167,512	105,767	75,463	61,745	30,304
General and administrative expenses	46,542	32,810	21,967	13,732	10,843
Other:					
Interest income	27,620	8,713	466	18,907	8,247
Unrealized fair value gain (loss) on trading securities	3,550	(2,934)	(719)	6,484	(2,215)
Foreign exchange gain (loss)	199	(1,891)	358	2,090	(2,249)
Loss before income taxes	$ (182,685)	$ (125,255)	$ (78,888)	$ (57,430)	$ (46,367)

Revenue

Revenue decreased by $9.4 million in the year ended December 31, 2023 as compared to the same period in 2022. The decrease was primarily due to the Neurocrine Collaboration; all performance obligations associated with the upfront payment were completed in March 2022, resulting in a decrease in revenue of $0.4 million and the research component of our collaboration was completed in June 2022, resulting in a decrease in research and development services revenue of $1.9 million. In addition, we recognized a $7.1 million milestone under the Neurocrine Collaboration in 2022, whereas no milestones were recognized under this collaboration in 2023.

Revenue decreased by $9.0 million in the year ended December 31, 2022 as compared to the same period in 2021. The decrease was primarily due to the Neurocrine Collaboration; all performance obligations associated with the upfront payment were completed in March 2022, resulting in a decrease in revenue of $3.3 million and the research component of our collaboration was completed in June 2022, resulting in a decrease in research and development services revenue of $4.5 million. In addition, we recognized a $3.0 million milestone under our Pacira Agreement in 2021, whereas no milestones were recognized under this agreement in 2022.

Research and Development Expenses

The following table summarizes research and development expenses for the years ended December 31, 2023, 2022 and 2021 together with changes in those items (in thousands):

	Year Ended December 31,			Change 2023 vs. 2022	Change 2022 vs. 2021
	2023	2022	2021	Increase/(Decrease)	Increase/(Decrease)
Direct external costs:					
XEN1101	$ 89,303	$ 37,367	$ 21,664	$ 51,936	$ 15,703
XEN496	5,152	14,765	13,017	(9,613)	1,748
Pre-clinical, discovery and other programs	15,552	12,711	13,342	2,841	(631)
Indirect costs:					
Personnel-related (including stock-based compensation)	45,981	32,447	21,225	13,534	11,222
Facilities and other unallocated research and development expenses	11,524	8,477	6,215	3,047	2,262
Research and development expenses	$ 167,512	$ 105,767	$ 75,463	$ 61,745	$ 30,304

Research and development expenses increased by $61.7 million in the year ended December 31, 2023 as compared to the same period in 2022. The increase was primarily attributable to our XEN1101 program as well as personnel-related costs due to increased headcount to support late-stage development and stock-based compensation expense due to an increase in the number of options granted at a higher fair value, partially offset by a decrease in spend on XEN496. The increase for XEN1101 is driven by ongoing site initiation and patient enrollment in our Phase 3 epilepsy clinical trials, increase in manufacturing activities to support current and future clinical trials and a potential NDA submission, as well as the completion of our X-NOVA Phase 2 MDD clinical trial. The decrease in XEN496 was attributed to decreased external costs to support the EPIK clinical trial and open label extension as a result of our decision to no longer pursue the clinical development of XEN496.

Research and development expenses increased by $30.3 million in the year ended December 31, 2022 as compared to the same period in 2021. The increase was primarily attributable to our XEN1101 program and personnel-related costs due to increased headcount to support late-stage development and stock-based compensation expense due to an increase in the number of options granted at a higher fair value. The increase for XEN1101 includes expenses related to the initiation of our Phase 3 epilepsy clinical trials, ongoing costs to support the X-TOLE open label extension, and our X-NOVA Phase 2 MDD clinical trial.

General and Administrative Expenses

The following table summarizes general and administrative expenses for the years ended December 31, 2023, 2022 and 2021 together with changes in those items (in thousands):

	Year Ended December 31,			Change 2023 vs. 2022	Change 2022 vs. 2021
	2023	2022	2021	Increase/(Decrease)	Increase/(Decrease)
Personnel-related (including stock-based compensation)	$ 32,166	$ 22,814	$ 14,123	$ 9,352	$ 8,691
Professional and consulting fees	8,760	5,189	4,367	3,571	822
Other	5,616	4,807	3,477	809	1,330
General and administrative expenses	$ 46,542	$ 32,810	$ 21,967	$ 13,732	$ 10,843

General and administrative expenses increased by $13.7 million in the year ended December 31, 2023 as compared to the same period in 2022. The increase was primarily attributable to personnel-related costs due to increased headcount to support our expanding research and development activities and stock-based compensation expense due to an increase in the number of options granted at a higher fair value as well as higher professional and consulting fees.

General and administrative expenses increased by $10.8 million in the year ended December 31, 2022 as compared to the same period in 2021. The increase was primarily attributable to personnel-related costs due to increased headcount to support our expanding research and development activities and stock-based compensation expense due to an increase in the number of options granted at a higher fair value as well as higher recruitment fees, insurance premiums, and higher professional and consulting fees.

Other Income

The following table summarizes our other income for the years ended December 31, 2023, 2022 and 2021 together with changes in those items (in thousands):

	Year Ended December 31,			Change 2023 vs. 2022	Change 2022 vs. 2021
	2023	2022	2021	Increase/(Decrease)	Increase/(Decrease)
Interest income	$ 27,620	$ 8,713	$ 466	$ 18,907	$ 8,247
Unrealized fair value gain (loss) on trading securities	3,550	(2,934)	(719)	6,484	(2,215)
Foreign exchange gain (loss)	199	(1,891)	358	2,090	(2,249)
Other income	$ 31,369	$ 3,888	$ 105	$ 27,481	$ 3,783

Other income increased by $27.5 million in the year ended December 31, 2023 as compared to the same period in 2022. The increase was primarily attributable to an $18.9 million increase in interest income driven by a higher balance of marketable securities and an increase in market yields on investments. In addition, there was a $6.5 million increase in the unrealized fair value gain on trading securities due to changes in market yields on trading securities, partially offset by a lower balance of trading securities. There was also a $2.1 million change in the foreign exchange gain (loss) due to fluctuations in the value of the Canadian dollar and a lower balance of cash and cash equivalents denominated in Canadian dollars.

Other income increased by $3.8 million in the year ended December 31, 2022 as compared to the same period in 2021. The increase was primarily attributable to an $8.2 million increase in interest income driven by a higher balance of marketable securities and an increase in market yields on investments. The increase was partially offset by a $2.2 million increase in foreign exchange loss due to a higher balance of cash and cash equivalents denominated in Canadian dollars and a decline in the value of the Canadian dollar, and a $2.2 million increase in the unrealized loss on the fair value of trading securities due to a higher balance of trading securities and increase in market yields on investments.

Liquidity and Capital Resources

Sources of Liquidity

To date, we have financed our operations primarily through the sale of equity securities, funding received from collaboration and license agreements, and debt financing. Since our initial public offering through December 31, 2023, we have raised aggregate net cash proceeds of more than $1.3 billion primarily from the issuance of equity securities, including net proceeds of approximately $324.0 million from the sale of common shares and pre-funded warrants in a public offering in November 2023. As of December 31, 2023, we had cash and cash equivalents and marketable securities of $930.9 million.

Except for any obligations of our collaborators to make milestone payments under our agreements with them, we do not have any committed external sources of capital. Until such time as we can generate substantial product revenue, if ever, we expect to finance our cash needs through a combination of collaboration agreements and equity or debt financings.

We entered into an "at-the-market" equity offering sales agreement in August 2020, amended as of March 2022, with Jefferies LLC, or Jefferies, and Stifel, Nicolaus & Company, Incorporated, or Stifel, pursuant to which we may sell our common shares from time to time. In January 2021, we sold an aggregate of 733,000 common shares for proceeds of $10.7 million, net of commissions and transaction expenses pursuant to a prospectus supplement filed with the SEC on August 6, 2020, or the August 2020 ATM. We may sell common shares having gross proceeds of up to $250.0 million, from time to time, pursuant to a new prospectus supplement filed with the SEC on March 1, 2022, or the March 2022 ATM, replacing the August 2020 ATM. As of December 31, 2023, an aggregate of 855,685 common shares have been sold for proceeds of $29.5 million, net of commissions and transaction expenses, under the March 2022 ATM.

Funding Requirements

We have incurred significant operating losses since inception. As of December 31, 2023, we had an accumulated deficit of $665.1 million. We expect to continue to incur significant expenses in excess of our revenue and expect to incur operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We expect to 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 studies for our current and prospective product candidates; initiate additional pre-clinical, clinical or other studies for our product candidates; 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; hire and retain additional personnel; 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 1st Order Pharmaceuticals, Inc and other third parties; maintain, protect and expand our intellectual property portfolio; establish a sales, marketing, distribution and other commercial infrastructure to commercialize any products for which we may obtain marketing approval; create additional infrastructure and incur additional costs 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 future capital requirements are difficult to forecast and will depend on many factors, including:

- the scope, progress, results and costs of researching and developing our current product candidates, as well as other additional product candidates we may develop and pursue in the future;
- the timing of, and the costs involved in, obtaining marketing approvals for our product candidates and any other additional product candidates we may develop and pursue in the future;
- the number of future product candidates that we may pursue and their development requirements;
- if approved, the costs of commercialization activities for any product candidate that receives regulatory approval to the extent such costs are not the responsibility of an existing or future collaborator, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- subject to the receipt of regulatory approval, revenue, if any, received from commercial sales of our product candidates and any other additional product candidates we may develop and pursue in the future;

- whether our existing collaborations generate substantial milestone payments and, ultimately, royalties on future approved products for us;
- our ability to maintain existing collaborations and to establish new collaborations, licensing or other arrangements and the financial terms of such agreements;
- our headcount growth and associated costs as we expand our research and development and initiate pre-commercial and commercial activities;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patents, including litigation costs and the outcome of such litigation; and
- the ongoing costs of operating as a public company.

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. However, our estimates and assumptions may prove to be wrong, and we cannot guarantee that our existing capital resources will be sufficient to conduct and complete all of our anticipated research and development efforts and future commercialization efforts. Additionally, the process of testing drug candidates in clinical trials is costly, and the timing of progress in these trials remains uncertain. Further, inflation may affect our use of capital resources by increasing our cost of labor and research and development expenses. Our long-term funding requirements will consist of operational, capital, and manufacturing expenditures, including those contractual commitments described below. Because of the inherent risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of capital outflows and operating expenditures associated with our long-term anticipated pre-clinical studies and clinical trials.

Contractual Commitments

In April 2017, we acquired XEN1101 (previously known as 1OP2198) from 1st Order Pharmaceuticals, Inc., or 1st Order, pursuant to an asset purchase agreement. In August 2020, we and 1st Order amended the asset purchase agreement to amend certain definitions in the agreement and to modify the payment schedule for certain milestones. Through December 31, 2023, we have paid $2.0 million based on progress against these milestones. Future potential payments to 1st Order include up to $6.0 million in regulatory milestones. There are no royalty obligations to 1st Order.

We have operating leases for research laboratories and office space in Burnaby, British Columbia and office space in Needham, Massachusetts. The terms of the leases expire in June 2032 and November 2027, respectively. Amounts related to future lease payments for operating lease obligations as of December 31, 2023 totaled $12.5 million, with $1.7 million expected to be paid within the next 12 months.

Cash Flows

The following table shows a summary of our cash flows for the years ended December 31, 2023, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Net cash used in operating activities	$ (145,327)	$ (98,430)	$ (69,502)
Net cash used in investing activities	(117,170)	(296,003)	(246,770)
Net cash provided by financing activities	353,522	278,471	447,543

Operating Activities

For the year ended December 31, 2023, net cash used in operating activities totaled $145.3 million, compared to $98.4 million for the same period in 2022. The increase was primarily related to higher research and development and general and administrative expenses, and no revenue recognized in 2023. This was partially offset by higher interest income and changes in operating assets and liabilities.

For the year ended December 31, 2022, net cash used in operating activities totaled $98.4 million, compared to $69.5 million for the same period in 2021. The increase was primarily related to higher research and development and general and administrative expenses, and lower revenue recognized in connection with the Neurocrine Collaboration and the Pacira Agreement. This was partially offset by higher interest income and changes in operating assets and liabilities.

Investing Activities

For the year ended December 31, 2023, net cash used in investing activities totaled $117.2 million, compared to $296.0 million for the same period in 2022. The change was driven primarily by an increase in the redemption of marketable securities, net of purchases. This was partially offset by an increase in the purchases of property, plant and equipment.

For the year ended December 31, 2022, net cash used in investing activities totaled $296.0 million, compared to $246.8 million for the same period in 2021. The change was driven primarily by an increase in purchases of marketable securities, net of redemptions.

Financing Activities

For the year ended December 31, 2023, net cash provided by financing activities totaled $353.5 million, compared to $278.5 million for the same period in 2022. The increase was primarily related to net proceeds of $353.5 million in 2023 as compared to net proceeds of $277.8 million in 2022 from the issuance of common shares and pre-funded warrants.

For the year ended December 31, 2022, net cash provided by financing activities totaled $278.5 million, compared to $447.5 million for the same period in 2021. The decrease was primarily related to net proceeds of $277.8 million in 2022 as compared to net proceeds of $447.3 million in 2021 from the issuance of common shares and pre-funded warrants.

Related Party Transactions

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

Outstanding Share Data

As of February 26, 2024, we had 75,432,482 common shares issued and outstanding, outstanding pre-funded warrants to purchase an additional 2,173,081 common shares, outstanding stock options to purchase an additional 8,860,105 common shares and an outstanding warrant to purchase an additional 40,000 common shares.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

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

Foreign currency risk

As of December 31, 2023, we had U.S. dollar denominated cash and cash equivalents and marketable securities of $907.1 million and Canadian dollar denominated cash and cash equivalents and marketable securities of CAD$31.5 million.

We are subject to foreign currency exchange rate risk in part, as a result of entering into transactions denominated in currencies other than U.S. dollars, particularly those denominated in Canadian dollars. We also hold Canadian dollar denominated cash and cash equivalents, accounts receivable and accounts payable.

Changes in foreign currency exchange rates can create significant foreign exchange gains or losses to us. We do not currently hedge our exposure and thus assume the risk of future gains or losses on the amounts of Canadian dollars held. While we have experienced increased foreign exchange fluctuations in recent periods, we do not believe that an immediate 10% increase or decrease in the relative value of the U.S. dollar to the Canadian dollar would have a material effect on our operating results.

Interest rate sensitivity

As of December 31, 2023, we had cash and cash equivalents and marketable securities of $930.9 million. Our interest rate sensitivity is primarily attributable to our cash and cash equivalents and marketable securities. A 100 basis point, or 1%, unfavorable change in interest rates would have resulted in approximately a $5.7 million decrease in the fair value of our marketable securities as of December 31, 2023. We do not enter into investments for speculative purposes and have not used any derivative financial instruments to manage interest rate exposure.

Inflation risk

Inflation may generally affect us by increasing our cost of labor and research and development expenses. While we have experienced increased operating expenses in recent periods, which we believe are due in part to the recent growth in inflation, we do not believe that inflation has had a material effect on our business, financial condition or results of operations during the year ended December 31, 2023; however, operating expenses may continue to increase in future periods due to inflation.

Item 8. Financial Statements and Supplementary Data

XENON PHARMACEUTICALS INC.
Index to Consolidated Financial Statements

Year ended December 31, 2023

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
Xenon Pharmaceuticals Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Xenon Pharmaceuticals Inc. (the Company) as of December 31, 2023 and 2022, the related consolidated statements of operations and comprehensive loss, shareholders' equity, and cash flows for each of the years in the three year period ended December 31, 2023, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2023 and 2022, and the results of its operations and its cash flows for each of the years in the three year period ended December 31, 2023, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2023, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission, and our report dated February 29, 2024 expressed an unqualified opinion on the effectiveness of the Company's internal control over financial reporting.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

The critical audit matters are matters arising from the current period audit of the consolidated financial statements that were communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. We determined that there are no critical audit matters.

/s/ KPMG LLP

Chartered Professional Accountants

We have served as the Company's auditor since 1999.

Vancouver, Canada
February 29, 2024

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
Xenon Pharmaceuticals Inc.:

Opinion on Internal Control Over Financial Reporting

We have audited Xenon Pharmaceuticals Inc.'s (the Company) internal control over financial reporting as of December 31, 2023, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission. In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2023, based on criteria established in *Internal Control – Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2023 and 2022, the related consolidated statements of operations and comprehensive loss, shareholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2023, and the related notes (collectively, the consolidated financial statements), and our report dated February 29, 2024 expressed an unqualified opinion on those consolidated financial statements.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audit also included performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ KPMG LLP

Chartered Professional Accountants

Vancouver, Canada
February 29, 2024

XENON PHARMACEUTICALS INC.
Consolidated Balance Sheets
(Expressed in thousands of U.S. dollars except share amounts)

	December 31, 2023	December 31, 2022
Assets		
Current assets:		
Cash and cash equivalents	$ 148,643	$ 57,242
Marketable securities (note 6)	489,439	534,845
Accounts receivable	874	986
Prepaid expenses and other current assets	6,006	7,225
	644,962	600,298
Marketable securities, long-term (note 6)	292,792	128,682
Operating lease right-of-use asset, net (note 8)	9,193	10,406
Property, plant and equipment, net (note 7)	9,653	6,500
Deferred tax assets (note 13)	802	509
Prepaid expenses, long-term	7,396	7,751
Total assets	$ 964,798	$ 754,146
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable and accrued expenses (note 9)	$ 25,974	$ 22,214
Operating lease liability (note 8)	1,299	488
	27,273	22,702
Operating lease liability, long-term (note 8)	9,604	9,947
Total liabilities	$ 36,877	$ 32,649
Shareholders' equity:		
Common shares, without par value; unlimited shares authorized; issued and outstanding: 75,370,977 (December 31, 2022 - 62,587,701) (note 10)	$ 1,436,374	$ 1,065,136
Additional paid-in capital	156,764	142,108
Accumulated deficit	(665,140)	(482,747)
Accumulated other comprehensive loss	(77)	(3,000)
Total shareholders' equity	$ 927,921	$ 721,497
Total liabilities and shareholders' equity	$ 964,798	$ 754,146
Commitments and contingencies (note 12)		

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

XENON PHARMACEUTICALS INC.
Consolidated Statements of Operations and Comprehensive Loss
(Expressed in thousands of U.S. dollars except share and per share amounts)

	Year Ended December 31,		
	2023	2022	2021
Revenue (note 11)	$ —	$ 9,434	$ 18,437
Operating expenses:			
Research and development	167,512	105,767	75,463
General and administrative	46,542	32,810	21,967
	214,054	138,577	97,430
Loss from operations	(214,054)	(129,143)	(78,993)
Other income (expense):			
Interest income	27,620	8,713	466
Unrealized fair value gain (loss) on trading securities	3,550	(2,934)	(719)
Foreign exchange gain (loss)	199	(1,891)	358
	31,369	3,888	105
Loss before income taxes	(182,685)	(125,255)	(78,888)
Income tax recovery (expense) (note 13)	292	(118)	6
Net loss	(182,393)	(125,373)	(78,882)
Net loss attributable to preferred shareholders	—	(437)	(1,795)
Net loss attributable to common shareholders	$ (182,393)	$ (124,936)	$ (77,087)
Other comprehensive income (loss):			
Unrealized gain (loss) on available-for-sale securities (note 6)	$ 2,923	$ (2,010)	$ —
Comprehensive loss	$ (179,470)	$ (127,383)	$ (78,882)
Net loss per common share (note 4):			
Basic and diluted	$ (2.73)	$ (2.06)	$ (1.77)
Weighted-average common shares outstanding (note 4):			
Basic and diluted	66,889,005	60,542,142	43,627,452

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

XENON PHARMACEUTICALS INC.
Consolidated Statements of Shareholders' Equity
(Expressed in thousands of U.S. dollars except share amounts)

	Convertible preferred shares		Common shares		Additional paid-in capital	Accumulated deficit	Accumulated other comprehensive loss	Total shareholders' equity
	Shares	*Amount*	*Shares*	*Amount*				
Balance as of December 31, 2020	1,016,000	$ 7,732	35,012,125	$ 397,748	$ 45,357	$ (278,492)	$ (990)	$ 171,355
Net loss for the year	—	—	—	—	—	(78,882)	—	(78,882)
Issuance of common shares and pre-funded warrants, net of issuance costs (note 10a and note 10e)	—	—	16,143,472	381,567	65,716	—	—	447,283
Stock-based compensation expense (note 10c)	—	—	—	—	10,017	—	—	10,017
Issued pursuant to exercise of stock options	—	—	479,155	3,855	(3,595)	—	—	260
Balance as of December 31, 2021	1,016,000	$ 7,732	51,634,752	$ 783,170	$ 117,495	$ (357,374)	$ (990)	$ 550,033
Net loss for the year	—	—	—	—	—	(125,373)	—	(125,373)
Issuance of common shares and pre-funded warrants, net of issuance costs (note 10a and note 10e)	—	—	9,357,348	268,379	9,387	—	—	277,766
Conversion of preferred shares to common shares (note 10d)	(1,016,000)	(7,732)	1,016,000	7,732	—	—	—	—
Stock-based compensation expense (note 10c)	—	—	—	—	20,376	—	—	20,376
Issued pursuant to exercise of stock options	—	—	579,601	5,855	(5,150)	—	—	705
Other comprehensive loss (note 6)	—	—	—	—	—	—	(2,010)	(2,010)
Balance as of December 31, 2022	—	$ —	62,587,701	$ 1,065,136	$ 142,108	$ (482,747)	$ (3,000)	$ 721,497
Net loss for the year	—	—	—	—	—	(182,393)	—	(182,393)
Issuance of common shares and pre-funded warrants, net of issuance costs (note 10a and note 10e)	—	—	10,701,842	330,010	23,477	—	—	353,487
Conversion of pre-funded warrants to common shares (note 10e)	—	—	1,700,000	35,913	(35,913)	—	—	—
Stock-based compensation expense (note 10c)	—	—	—	—	32,372	—	—	32,372
Issued pursuant to exercise of stock options	—	—	381,434	5,315	(5,280)	—	—	35
Other comprehensive income (note 6)	—	—	—	—	—	—	2,923	2,923
Balance as of December 31, 2023	—	$ —	75,370,977	$ 1,436,374	$ 156,764	$ (665,140)	$ (77)	$ 927,921

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

XENON PHARMACEUTICALS INC.
Consolidated Statements of Cash Flows
(Expressed in thousands of U.S. dollars)

	Year Ended December 31,		
	2023	2022	2021
Operating activities:			
Net loss	$ (182,393)	$ (125,373)	$ (78,882)
Items not involving cash:			
Depreciation	3,541	1,624	906
Deferred income tax (recovery) expense	(292)	(44)	58
Stock-based compensation	32,372	20,376	10,017
Unrealized foreign exchange (gain) loss	(640)	2,729	327
Unrealized fair value (gain) loss on trading securities	(3,550)	2,934	719
Changes in operating assets and liabilities:			
Accounts receivable	130	1,757	(459)
Prepaid expenses and other current assets	1,574	(10,495)	(1,517)
Accounts payable and accrued expenses	3,931	8,062	2,971
Deferred revenue	—	—	(3,642)
Net cash used in operating activities	(145,327)	(98,430)	(69,502)
Investing activities:			
Purchases of property, plant and equipment	(5,617)	(2,894)	(2,050)
Purchase of marketable securities	(793,907)	(551,137)	(389,474)
Proceeds from marketable securities	682,354	258,028	144,754
Net cash used in investing activities	(117,170)	(296,003)	(246,770)
Financing activities:			
Issuance of common shares and pre-funded warrants, net of issuance costs (note 10a and note 10e)	353,487	277,766	447,283
Issuance of common shares pursuant to exercise of stock options	35	705	260
Net cash provided by financing activities	353,522	278,471	447,543
Effect of exchange rate changes on cash and cash equivalents	376	(2,484)	(592)
Increase (decrease) in cash and cash equivalents	91,401	(118,446)	130,679
Cash and cash equivalents, beginning of year	57,242	175,688	45,009
Cash and cash equivalents, end of year	$ 148,643	$ 57,242	$ 175,688
Supplemental disclosures:			
Cash paid for operating lease	$ 1,624	$ 919	$ 824
Cash received for lease incentives	1,489	—	—
Supplemental disclosures of non-cash transactions:			
Fair value of stock options exercised on a cashless basis	5,250	4,491	3,349
Fair value of pre-funded warrants exercised	35,913	—	—
Purchases of property, plant and equipment included in accounts payable and accrued expenses	—	391	—
Right-of-use asset obtained in exchange for new operating lease liability (note 8)	—	3,019	—
Increase in operating lease liability and accounts receivable related to lease incentives claimed in the period (note 8)	—	—	493
Increase in operating lease right-of-use asset and operating lease liability related to lease amendments (note 8)	—	—	5,248

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

1. Nature of the business:

Xenon Pharmaceuticals Inc. (the "Company"), incorporated in 1996 under the predecessor to the Business Corporations Act (British Columbia) and continued federally in 2000 under the Canada Business Corporations Act, is a neuroscience-focused biopharmaceutical company committed to improving the lives of people living with neurological and psychiatric disorders.

The Company has incurred significant operating losses since inception. As of December 31, 2023, the Company had an accumulated deficit of $665,140 and a net loss of $182,393 for the year ended December 31, 2023. Management expects to continue to incur significant expenses in excess of revenue and to incur operating losses for the foreseeable future. To date, the Company has financed its operations primarily through the sale of equity securities, funding received from collaboration and license agreements, and debt financings.

Until such time as the Company can generate substantial product revenue, if ever, management expects to finance the Company's cash needs through a combination of collaboration agreements, equity and debt financings. The continuation of research and development activities and the future commercialization of its products are dependent on the Company's ability to successfully raise additional funds when needed. It is not possible to predict either the outcome of future research and development programs or the Company's ability to continue to fund these programs in the future.

2. Basis of presentation:

These consolidated financial statements are presented in U.S. dollars and have been prepared in accordance with United States generally accepted accounting principles ("U.S. GAAP").

The Company has one wholly-owned subsidiary as of December 31, 2023, Xenon Pharmaceuticals USA Inc., which was incorporated in Delaware on December 2, 2016.

These consolidated financial statements include the accounts of the Company and its wholly-owned subsidiary. All intercompany transactions and balances have been eliminated on consolidation.

3. Significant accounting policies:

(a) Use of estimates:

The preparation of the consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. Significant areas of estimates include, but are not limited to, revenue recognition including estimated timing of completion of performance obligations and the determination of stock-based compensation. These estimates and assumptions take into account historical and forward-looking factors that the Company believes are reasonable. Estimates and assumptions are reviewed quarterly. All revisions to accounting estimates are recognized in the period in which the estimates are revised and in any future periods affected.

(b) Cash and cash equivalents:

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

(c) Marketable securities:

Marketable securities are debt securities with original maturities exceeding three months and accrue interest based on a fixed interest rate for the term. Effective July 1, 2022, the Company classifies its marketable securities as either trading securities or available-for-sale securities. Marketable securities are carried at fair value.

Fair value gains and losses for marketable securities classified as trading securities are recorded through the consolidated statement of operations. These securities are classified as current assets as the Company has the intent and ability to convert these securities into cash without penalty within the next 12 months.

Unrealized fair value gains and losses for marketable securities classified as available-for-sale are recorded through other comprehensive income (loss) in shareholders' equity. When the fair value of an available-for-sale security falls below the amortized cost basis it is evaluated to determine if any of the decline in value is attributable to credit loss. Decreases in fair value attributable to credit loss are recorded directly to the consolidated statement of operations with a corresponding allowance for credit losses, limited to the amount that the fair value is less than the amortized cost basis. If the credit quality subsequently improves the allowance is reversed up to a maximum of the previously recorded credit losses. When the Company intends to sell an impaired available-for-sale security, or if it is more likely than not that the Company will be required to sell the security prior to recovering the amortized cost basis, the entire fair value adjustment will immediately be recognized in the consolidated statement of operations with no corresponding allowance for credit losses. Realized gains and losses and credit losses, if any, on available-for-sale securities are included in interest income, based on the specific identification method. Available-for-sale securities are also adjusted for amortization of premiums and accretion of discounts to maturity, with such amortization and accretion included within interest income. Available-for-sale securities with a remaining maturity date greater than one year are classified as non-current assets.

(d) Intellectual property:

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

(e) Property, plant and equipment:

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

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

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

(f) Impairment of long-lived assets:

The Company monitors its long-lived assets for indicators of impairment. If such indicators are present, the Company assesses the recoverability of affected assets by determining whether the carrying value of such assets is less than the sum of the undiscounted future cash flows of the assets. If such assets are found not to be recoverable, the Company measures the amount of such impairment by comparing the carrying value of the assets to the fair value of the assets, with the fair value generally determined based on the present value of the expected future cash flows associated with the assets. No impairment of long-lived assets was noted during the years ended December 31, 2023, 2022 and 2021.

(g) Leases:

Leases classified as operating leases are recorded as lease liabilities based on the present value of minimum lease payments over the lease term, discounted using the lessor’s rate implicit in the lease or the Company’s incremental borrowing rate, if the lessor’s implicit rate is not readily determinable. The lease term includes all periods covered by renewal and termination options where the Company is reasonably certain to exercise the renewal options or not to exercise the termination options. Corresponding right-of-use assets are recognized consisting of the lease liabilities, initial direct costs and any lease incentive payments. Lease liabilities are drawn down as lease payments are made and right-of-use assets are depreciated over the term of the lease. Operating lease expenses are recognized on a straight-line basis over the term of the lease, consisting of interest accrued on the lease liability and depreciation of the right-of-use asset, adjusted for changes in index-based variable lease payments in the period of change. Lease payments on short-term operating leases with lease terms twelve months or less are expensed on a straight-line basis over the lease term. The Company has elected to not separate non-lease elements embedded in its lease agreements.

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

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash and cash equivalents and marketable securities. The Company's investments are limited to investment-grade securities with strong credit ratings with the objective to preserve capital and maintain liquidity. Cash and cash equivalents were held at major financial institutions in Canada and the United States which may at times be in excess of federally insured limits. The Company does not believe that it is subject to credit risk beyond the standard credit risk associated with commercial banking relationships.

Neurocrine Biosciences, Inc. ("Neurocrine Biosciences") accounted for 100% of revenue recognized for the year ended December 31, 2022. Neurocrine Biosciences and Pacira BioSciences, Inc. (“Pacira BioSciences”) accounted for 84% and 16% of revenue recognized for the year ended December 31, 2021, respectively.

(i) Financial instruments and fair value:

The Company measures certain financial instruments and other items at fair value.

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

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

Assets and liabilities are classified based on the lowest level of input that is significant to the fair value measurements. Changes in the observability of valuation inputs may result in a reclassification of levels for certain securities within the fair value hierarchy. The carrying amount of accounts receivable, accounts payable and accrued expenses approximates fair value due to the nature and short-term of those instruments. The Company’s cash and cash equivalents and marketable securities are measured at fair value on a recurring basis and the level of fair value hierarchy utilized is described in note 5.

(j) Revenue recognition:

The Company recognizes the amount of revenue to which it expects to be entitled, for the transfer of promised goods or services to customers under a five-step model: (i) identify contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when or as a performance obligation is satisfied.

Collaboration agreements may require the Company to deliver various rights and/or services, including intellectual property rights or licenses and research and development services. Under such collaboration agreements, the Company is generally eligible to receive non-refundable upfront payments, funding for research and development services, milestone payments, and royalties.

In contracts where the Company has more than one performance obligation to provide its customer with goods or services, each performance obligation is evaluated to determine whether it is distinct based on whether (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available and (ii) the good or service is separately identifiable from other promises in the contract. The consideration under the contract is then allocated between the distinct performance obligations based on their respective relative standalone selling prices. The estimated standalone selling price of each deliverable reflects the Company’s best estimate of what the selling price would be if the deliverable was regularly sold on a standalone basis and is determined by reference to market rates for the good or service when sold to others or by using an adjusted market assessment approach if selling price on a standalone basis is not available.

The consideration allocated to each distinct performance obligation is recognized as revenue when control is transferred to the customer for the related goods or services. Consideration in exchange for research and development services performed by the Company on behalf of the licensee is recognized upon performance of such activities at rates consistent with prevailing market rates. Consideration associated with at-risk substantive performance milestones, including sales-based milestones, is recognized as revenue using the most likely amount method when it is probable that a significant reversal of the cumulative revenue recognized will not occur. Sales-based royalties received in connection with licenses of intellectual property are subject to a specific exception in the revenue standards, whereby the consideration is not included in the transaction price and recognized in revenue until the customer's subsequent sales or usages occur.

(k) Research and development costs:

Research and development costs are expensed in the period incurred.

Research and development expenses consist of costs incurred in performing research and development activities, including personnel-related expenses, consisting of salaries, benefits and stock-based compensation for employees engaged in scientific research and development, third-party expenses incurred in connection with the pre-clinical and clinical development of product candidates including under agreements with clinical research organizations, third-party expenses relating to formulation, process development and manufacture of drug substance and drug product for use in pre-clinical testing and clinical trials, third-party acquisition, license and collaboration fees, laboratory consumables and certain indirect costs incurred in support of overall research and development activities, including facilities, depreciation and information technology costs. The amount of expenses recognized in a period related to service agreements is based on the work performed using the accrual basis of accounting. Third-party service providers generally provide estimates of proportionate performance to allow the Company to determine an appropriate accrual. When determining the adequacy of an accrual, the Company analyzes progress based on the level of services performed, progress of the studies, including the phase or completion of events, and contracted costs. Payments made to third parties under these arrangements in advance of the receipt of the related services are recorded as prepaid expenses until the services are rendered. Prepaid expenses are recorded as current or non-current assets based on the expected timing of services.

(l) Stock-based compensation:

The Company grants stock options to employees, consultants, directors and officers pursuant to stock option plans described in note 10c.

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

(m) Foreign currency translation:

The functional and reporting currency of the Company and its subsidiary is the U.S. dollar. Monetary assets and liabilities denominated in a currency other than the U.S. dollar are re-measured into U.S. dollars at the exchange rate prevailing as of the balance sheet date. Non-monetary assets and liabilities acquired in a currency other than U.S. dollars are translated at historical exchange rates prevailing at each transaction date.

Revenue and expense transactions are translated at the approximate exchange rate prevailing on the date of transaction. Exchange gains and losses on translation are included in the consolidated statements of operations and comprehensive income (loss) as foreign exchange gain (loss).

(n) Income taxes:

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

(o) Segment and geographic information:

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

(p) Recent accounting pronouncements:

From time to time, new accounting pronouncements are issued by the Financial Accounting Standards Board or other standard setting bodies that the Company adopts as of the specified effective date. The Company has evaluated recently issued accounting pronouncements and, based on preliminary assessment, does not believe any will have a material impact on the Company's financial statements.

4. Net income (loss) per common share:

Basic net income (loss) per common share is calculated using the two-class method required for participating securities which includes the Series 1 Preferred Shares as a separate class. The convertible preferred shares entitle the holders to participate in dividends and in earnings and losses of the Company on an equivalent basis as common shares. Accordingly, undistributed earnings (losses) are allocated to common shares and participating preferred shares based on the weighted-average shares of each class outstanding during the period. In March 2022, the outstanding 1,016,000 Series 1 Preferred Shares were converted and exchanged for an equal number of common shares of the Company (note 10d).

The weighted average number of common shares used in the basic and diluted net income (loss) per common share calculations includes the weighted-average pre-funded warrants outstanding during the period as they are exercisable at any time for nominal cash consideration.

The treasury stock method is used to compute the dilutive effect of the Company's stock options and warrants. Under this method, the incremental number of common shares used in computing diluted net income (loss) per common share is the difference between the number of common shares assumed issued and purchased using assumed proceeds.

The if-converted method is used to compute the dilutive effect of the Company's convertible preferred shares. Under the if-converted method, dividends on the preferred shares, if applicable, are added back to earnings attributable to common shareholders, and the preferred shares and paid-in kind dividends are assumed to have been converted at the share price applicable at the end of the period. The if-converted method is applied only if the effect is dilutive.

For the years ended December 31, 2023, 2022 and 2021, diluted net loss per share attributable to common shareholders is the same as basic net loss per share attributable to common shareholders, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

5. Fair value of financial instruments:

The level of the fair value hierarchy utilized to determine the fair value of cash and cash equivalents and marketable securities consisted of the following:

	December 31, 2023				December 31, 2022			
	Level 1	Level 2	Level 3	Total	Level 1	Level 2	Level 3	Total
Cash and cash equivalents								
Cash and money market fund	$148,643	$ —	$ —	$148,643	$ 57,242	$ —	$ —	$ 57,242
Marketable securities								
Guaranteed investment certificates	7,684	—	—	7,684	14,953	—	—	14,953
U.S. treasuries	252,982	—	—	252,982	322,851	—	—	322,851
U.S. government securities	—	97,912	—	97,912	—	32,479	—	32,479
Commercial paper	—	119,108	—	119,108	—	150,560	—	150,560
Corporate debt securities	—	304,545	—	304,545	—	142,684	—	142,684
Total	$409,309	$521,565	$ —	$930,874	$395,046	$325,723	$ —	$720,769

The fair values of the Company's U.S. government securities, commercial paper and corporate debt securities are based on prices obtained from independent pricing sources. Securities with validated quotes from pricing services are reflected within Level 2, as they are primarily based on observable pricing for similar assets or other market observable inputs. Typical inputs used by these pricing services include, but are not limited to, reported trades, benchmark yields, issuer spreads, bids, offers or estimates of cash flow, prepayment spreads and default rates.

As of December 31, 2023 and December 31, 2022, the Company does not hold any securities classified as Level 3.

6. Marketable securities:

As of December 31, 2023, the Company had $13,867 of trading securities and $768,364 of available-for-sale securities (December 31, 2022 – $276,642 and $386,885, respectively). Amortized cost, unrealized gain (losses) recognized in accumulated other comprehensive income (loss) and fair value of available-for-sale securities consisted of the following:

	December 31, 2023			December 31, 2022		
	Amortized Cost	Unrealized Gain (Loss)	Fair Value	Amortized Cost	Unrealized Loss	Fair Value
Contractual maturity of 0 to 1 years:						
Guaranteed investment certificates	$ 7,549	$ 135	$ 7,684	$ 14,953	$ —	$ 14,953
U.S. treasuries	192,193	(249)	191,944	78,880	(837)	78,043
U.S. government securities	98,092	(180)	97,912	5,793	(20)	5,773
Commercial paper	119,041	67	119,108	150,560	—	150,560
Corporate debt securities	58,824	100	58,924	8,942	(68)	8,874
Contractual maturity of 1 to 3 years:						
U.S. treasuries	53,294	243	53,537	60,354	(958)	59,396
U.S. government securities	—	—	—	26,741	(35)	26,706
Corporate debt securities	238,458	797	239,255	42,672	(92)	42,580
Total	$ 767,451	$ 913	$ 768,364	$ 388,895	$ (2,010)	$ 386,885

Allowance for credit losses or impairment on these marketable securities have not been recognized as these securities are high credit quality, investment grade securities that the Company does not intend to sell and will not be required to sell prior to their anticipated recovery, and the decline in fair value is primarily due to changes in interest rates.

7. Property, plant and equipment:

Property, plant and equipment consisted of the following:

	December 31,	
	2023	2022
Research equipment	$ 9,111	$ 8,921
Office furniture and equipment	1,285	868
Computer equipment	1,489	1,213
Leasehold improvements	9,019	4,203
Less: accumulated depreciation and amortization	(11,251)	(8,705)
Net book value	$ 9,653	$ 6,500

8. Leases:

The Company has an operating lease for research laboratories and office space in Burnaby, British Columbia which expires on June 30, 2032, and two renewal options for 5-years each which were not considered in the determination of the right-of-use asset and lease liability. The Company has an additional operating lease for office space in Needham, Massachusetts ("Needham Lease"), which commenced in October 2022. The Needham Lease is for a 62-month term and an option to terminate one year prior to the expiry date, which was not considered in the determination of the right-of-use asset and lease liability.

The cost components of the operating leases were as follows for the years ended December 31, 2023, 2022 and 2021:

	Year Ended December 31,		
	2023	2022	2021
Lease Cost			
Operating lease expense	$ 1,645	$ 1,126	$ 591
Variable lease expense[(1)]	787	774	751
Lease Term and Discount Rate			
Weighted average remaining lease term (years)	7.33	8.07	10.50
Weighted average discount rate	3.87%	3.97%	3.42%

(1) Variable lease costs are payments that vary because of changes in facts or circumstances and include common area maintenance and property taxes related to the premises. Variable lease costs are excluded from the calculation of minimum lease payments.

Future minimum lease payments as of December 31, 2023 were as follows:

Year ending December 31:	
2024	$ 1,698
2025	1,768
2026	1,837
2027	1,825
2028	1,126
2029 and thereafter	4,283
Total future minimum lease payments	$ 12,537
Less: imputed interest	(1,634)
Present value of lease liabilities	$ 10,903

9. Accounts payable and accrued expenses:

Accounts payable and accrued expenses consisted of the following:

	December 31,	
	2023	2022
Trade payables	$ 8,598	$ 8,491
Employee compensation, benefits, and related accruals	7,425	5,823
Consulting and contracted research	8,824	7,148
Professional fees	780	411
Other	347	341
Total	$ 25,974	$ 22,214

10. Share capital:

(a) Financing:

In August 2020, the Company entered into an "at-the-market" equity offering sales agreement, amended as of March 2022, with Jefferies LLC ("Jefferies") and Stifel, Nicolaus & Company, Incorporated ("Stifel") pursuant to which the Company may sell common shares from time to time. In January 2021, the Company sold an aggregate of 733,000 common shares for proceeds of $10,693, net of commissions and transaction expenses pursuant to a prospectus supplement filed in August 2020 ("August 2020 ATM"). The Company may sell common shares having gross proceeds of up to $250,000, from time to time, pursuant to a new prospectus supplement filed in March 2022 ("March 2022 ATM"), replacing the August 2020 ATM. As of December 31, 2023, the Company has sold an aggregate of 855,685 common shares for proceeds of $29,508, net of commissions and transaction expenses under the March 2022 ATM.

In March 2021, the Company completed an underwritten public offering of 5,135,135 common shares, including 810,810 common shares sold upon the full exercise of the underwriters' over-allotment option, at a public offering price of $18.50 per common share and pre-funded warrants to purchase 1,081,081 common shares at $18.4999 per pre-funded warrant (note 10e), with each pre-funded warrant having an exercise price of $0.0001. The public offering was completed in March 2021, and the Company received proceeds of $107,922, net of underwriting discounts, commissions and offering expenses.

In September 2021, in connection with the License and Collaboration Agreement with Neurocrine Biosciences entered in December 2019 and amended in January 2021 (the "Neurocrine Collaboration Agreement"), the Company executed a Share Purchase Agreement ("SPA") pursuant to which the Company issued 275,337 common shares for an aggregate purchase price of $5,500, or $19.9755 per common share, which represents a premium of $770 when measured at fair value on the date of issuance. In addition, in January 2022, the Company executed a SPA pursuant to which the Company issued 258,986 common shares for an aggregate purchase price of $8,250, or $31.855 per common share, which represents a premium of $374 when compared to the fair value of common shares on the date of issuance. The SPAs contain certain other customary terms and conditions, including mutual representations, warranties and covenants. For additional information regarding the Neurocrine Collaboration Agreement, refer to note 11a.

In October 2021, the Company completed an underwritten public offering of 10,000,000 common shares, including 1,525,423 common shares sold upon the full exercise of the underwriters' over-allotment option, at a public offering price of $29.50 per common share and pre-funded warrants to purchase 1,694,915 common shares at $29.4999 per pre-funded warrant (note 10e), with each pre-funded warrant having an exercise price of $0.0001. The public offering was completed in October 2021, and the Company received proceeds of $323,938, net of underwriting discounts, commissions and offering expenses.

In June 2022, the Company completed an underwritten public offering of 9,098,362 common shares, including 1,229,508 shares sold upon the full exercise of the underwriters' over-allotment option, at a public offering price of $30.50 per common share and pre-funded warrants to purchase 327,868 common shares at $30.4999 per pre-funded warrant (note 10e), with each pre-funded warrant having an exercise price of $0.0001. The public offering was completed in June 2022, and the Company received proceeds of $269,890, net of underwriting discounts, commissions and offering expenses.

In November 2023, the Company completed an underwritten public offering of 9,846,157 common shares, including 1,384,615 shares sold upon the full exercise of the underwriters' over-allotment option, at a public offering price of $32.50 per common share and pre-funded warrants to purchase 769,230 common shares at $32.4999 per pre-funded warrant (note 10e), with each pre-funded warrant having an exercise price of $0.0001. The public offering was completed in December 2023, and the Company received proceeds of $323,979, net of underwriting discounts, commissions and offering expenses.

(b) Authorized share capital:

The Company's authorized share capital consists of an unlimited number of common and preferred shares without par value.

(c) Stock-based compensation:

The Company has three equity incentive plans: (i) a pre-existing stock option plan (the "Amended and Restated Stock Option Plan"), (ii) the 2014 Equity Incentive Plan (the "2014 Plan") which was amended and restated in June 2020 and June 2022, and (iii) the 2019 Inducement Equity Incentive Plan (the "2019 Inducement Plan").

The Amended and Restated Stock Option Plan provided for the grant of stock options for the purchase of common shares to directors, officers, employees and consultants prior to the Company's initial public offering. The stock options granted under the Amended and Restated Stock Option Plan vest on a graduated basis over a four-year period or less and each option's maximum term is ten years. The 2014 Plan replaced the Amended and Restated Stock Option Plan. No further options will be granted under the Company's Amended and Restated Stock Option Plan. The Amended and Restated Stock Option Plan will continue to govern the stock options granted thereunder.

In June 2014, the shareholders of the Company approved the 2014 Plan, which was amended and replaced in June 2020 and June 2022 by the Amended and Restated 2014 Equity Incentive Plan (the "Amended and Restated 2014 Plan").

In September 2019, the board of directors of the Company adopted the 2019 Inducement Plan and, subject to the adjustment provisions of the 2019 Inducement Plan, reserved 400,000 of the Company's common shares for issuance pursuant to equity awards granted under the 2019 Inducement Plan. The 2019 Inducement Plan was adopted without shareholder approval in accordance with the applicable Nasdaq Listing Rules. The 2019 Inducement Plan provided for the grant of equity-based awards, including share options, share appreciation rights, restricted share awards, restricted share unit awards and performance share awards, and its terms are substantially similar to the Company's Amended and Restated 2014 Plan, including with respect to treatment of equity awards in the event of a "merger" or "change of control" as defined under the 2019 Inducement Plan, but with such other terms and conditions intended to comply with the Nasdaq inducement award exception or to comply with the Nasdaq acquisition and merger exception. The 2019 Inducement Plan was terminated in June 2020. No further options will be granted under the 2019 Inducement Plan, and the 2019 Inducement Plan will continue to govern the options granted thereunder.

The shareholders of the Company approved the Amended and Restated 2014 Plan amended in June 2020 and June 2022, amending certain provisions of the Company's 2014 Plan. The Amended and Restated 2014 Plan continues to permit the grant of stock-based compensation awards to directors, officers, employees and consultants of the Company and the issuance of restricted shares, restricted share units, share appreciation rights and performance shares. Under the Amended and Restated 2014 Plan, options granted generally vest on a graduated basis over a four-year period or less. The exercise price of the options is determined by the board of directors but must at least be equal to the fair market value of the common shares on the date of grant. Options may be exercised over a maximum term of ten years. The annual share increase provision of the 2014 Plan was eliminated and the number of common shares available for issuance was increased by 9,300,000 over the existing share reserve under the 2014 Plan. The number of common shares that can be issued through restricted share awards, restricted share unit awards, or performance share awards was amended to be limited to 1,000,000 common shares, in the aggregate. Other amendments were made to terms of the 2014 Plan with respect to repricing, change of control and payment of dividends and other distributions. As of December 31, 2023, a total of 3,460,724 common shares remain available for issuance pursuant to the Amended and Restated 2014 Plan.

The following table presents the summary of stock option activity for the period:

	Number of Options	Weighted Average Exercise Price ($)[1]	Aggregate Intrinsic Value
Outstanding, December 31, 2020	4,758,997	9.10	30,464
Granted	1,775,450	19.82	
Exercised[2]	(690,284)	7.34	11,306
Forfeited, cancelled or expired	(205,931)	13.01	
Outstanding, December 31, 2021	5,638,232	12.55	105,405
Granted	2,315,645	30.90	
Exercised[2]	(780,725)	9.47	19,651
Forfeited, cancelled or expired	(55,370)	24.50	
Outstanding, December 31, 2022	7,117,782	18.75	147,214
Granted	2,542,473	35.29	
Exercised[2]	(587,536)	13.58	14,526
Forfeited, cancelled or expired	(178,217)	31.49	
Outstanding, December 31, 2023	8,894,502	23.56	200,122
Exercisable, December 31, 2023	4,789,178	16.23	142,900

(1) Canadian dollar denominated stock options have been translated into U.S. dollars at a foreign exchange rate of 0.76 (2022 – 0.74 and 2021 – 0.79) as of December 31, 2023.

(2) During the year ended December 31, 2023, 4,320 (2022 – 68,930 and 2021 – 66,215) stock options were exercised for the same number of common shares in exchange for cash. In the same period, the Company issued 377,114 (2022 – 510,671 and 2021 – 412,940) common shares for the cashless exercise of 583,216 (2022 – 711,795 and 2021 – 624,069) stock options.

At December 31, 2023, stock options outstanding and exercisable had a weighted average remaining contractual life of 7.4 years and 6.2 years, respectively.

A summary of the Company's non-vested stock option activity and related information for the year ended December 31, 2023 is as follows:

	Number of Options	Weighted Average Grant Date Fair Value ($)
Non-vested, January 1, 2023	3,587,374	16.60
Granted	2,542,473	22.52
Vested	(1,847,714)	15.82
Forfeited or cancelled	(176,809)	18.62
Non-vested, December 31, 2023	4,105,324	20.53

The aggregate fair value of options vested during the year ended December 31, 2023 was $29,233 (2022 – $13,752 and 2021 – $8,271).

The fair value of stock options at the date of grant is estimated using the Black-Scholes option-pricing model which requires multiple subjective inputs. The risk-free interest rate of the options is based on the U.S. Treasury yield curve in effect at the date of grant for a term similar to the expected term of the option. The expected volatility is based on the historical volatility of the Company's common shares calculated based on a period of time commensurate with the expected term assumption. Expected life assumptions are based on the Company's historical data. The dividend yield is based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends. Forfeitures are recognized as they occur.

The weighted-average option pricing assumptions are as follows:

	Year Ended December 31,		
	2023	2022	2021
Average risk-free interest rate	3.93%	2.39%	1.16%
Expected volatility	69%	70%	68%
Average expected term (in years)	5.94	6.16	6.66
Expected dividend yield	0.00%	0.00%	0.00%
Weighted average fair value of options granted	$ 22.52	$ 19.78	$ 12.54

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

	Year Ended December 31,		
	2023	2022	2021
Research and development expenses	$ 13,067	$ 7,766	$ 3,734
General and administrative expenses	19,305	12,610	6,283
	$ 32,372	$ 20,376	$ 10,017

As of December 31, 2023, the unrecognized stock-based compensation expense related to the non-vested stock options was $70,691 which is expected to be recognized over a weighted-average period of 2.61 years.

(d) Exchange agreement with certain funds affiliated with BVF Partners L.P. (collectively, "BVF"):

In March 2018, the Company and BVF entered into an exchange agreement pursuant to which the Company issued to BVF 2,868,000 Series 1 Preferred Shares in exchange for 2,868,000 common shares which were subsequently cancelled by the Company. The Series 1 Preferred Shares were convertible into common shares on a one-for-one basis, subject to certain restrictions.

The Series 1 Preferred Shares ranked equally to the common shares in the event of liquidation, dissolution or winding up or other distribution of the assets of the Company among its shareholders and the holders of the Series 1 Preferred Shares were entitled to vote together with the common shares on an as-converted basis and as a single class, subject to certain restrictions.

The Series 1 Preferred Shares were recorded wholly as equity under ASC 480, with no bifurcation of conversion feature from the host contract, given that the Series 1 Preferred Shares cannot be cash settled and have no redemption features.

During the year ended December 31, 2018, BVF converted 1,852,000 Series 1 Preferred Shares in exchange for an equal number of common shares. In March 2022, the remaining outstanding 1,016,000 Series 1 Preferred Shares were exchanged for an equal number of common shares.

(e) Pre-funded warrants:

The following table summarizes the pre-funded warrants activity for the years ended December 31, 2023, 2022, and 2021:

	Date of issuance				
	March 2021	October 2021	June 2022	December 2023	Total
Outstanding, December 31, 2020	—	—	—	—	—
Issued	1,081,081	1,694,915	—	—	2,775,996
Exercised	—	—	—	—	—
Outstanding, December 31, 2021	1,081,081	1,694,915	—	—	2,775,996
Issued	—	—	327,868	—	327,868
Exercised	—	—	—	—	—
Outstanding, December 31, 2022	1,081,081	1,694,915	327,868	—	3,103,864
Issued	—	—	—	769,230	769,230
Exercised	(1,081,081)	(618,932)	—	—	(1,700,013)
Outstanding, December 31, 2023	—	1,075,983	327,868	769,230	2,173,081

In connection with underwritten public offerings completed in March 2021, October 2021, June 2022, and December 2023, the Company issued pre-funded warrants to purchase the equivalent number of common shares at $18.4999, $29.4999, $30.4999 and $32.4999 per pre-funded warrant, respectively, with each pre-funded warrant having an exercise price of $0.0001.

The pre-funded warrants are exercisable at the holder's discretion from the date of issuance until the date the pre-funded warrant is exercised in full. The Company may not affect the exercise of any pre-funded warrant, and a holder will not be entitled to exercise any portion of any pre-funded warrant that, upon giving effect to such exercise, would cause: (i) the aggregate number of common shares beneficially owned by such holder, together with its affiliates, to exceed 4.99% of the total number of common shares outstanding immediately after giving effect to the exercise; or (ii) the combined voting power of the Company's securities beneficially owned by such holder, together with its affiliates, to exceed 4.99% of the combined voting power of all of the Company's securities immediately outstanding after giving effect to the exercise, which percentage may be changed at the holder's election to a higher or lower percentage not in excess of 19.99% upon at least 61 days' notice to the Company.

Since the pre-funded warrants meet the condition for equity classification, proceeds from issuances of the pre-funded warrants of $23,477 (2022 – $9,387 and 2021 - 65,716), net of underwriting discounts, commissions and offering expenses, are recorded in additional paid-in capital. Upon exercise of the pre-funded warrants, the historical costs recorded in additional paid-in capital along with the exercise price collected from the holder are recorded in common shares. During the year ended December 31, 2023, the Company issued 1,700,000 common shares upon the exercise of 1,700,013 pre-funded warrants pursuant to a net exercise mechanism under the warrants. Pre-funded warrants to purchase 2,173,081 common shares (2022 – 3,103,864 and 2021 - 2,775,996) common shares are not included in the number of issued and outstanding common shares as of December 31, 2023.

(f) Warrant:

In August 2018, a warrant to purchase 40,000 (2022 - 40,000) common shares at a price per common share of $9.79 was issued. The warrant is immediately exercisable, contains a cashless exercise provision and expires in August 2028.

11. Collaboration agreements:

The Company has assessed each collaboration agreement in accordance with ASC 606 under the five-step model as described in note 3j, including recognition of non-refundable upfront payments. The Company generally recognizes revenue from non-refundable upfront payments over the estimated term of the performance obligation or period in which the underlying benefit is transferred to the customer. If non-refundable license fees have value to the customer on a standalone basis, separate from the undelivered performance obligations, they are recognized upon delivery. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

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

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

Regulatory milestone payments may include the following types of events:

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

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

The Company evaluates each arrangement that includes research and development and sales-based milestone payments to determine whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. Milestone payments that are not within the control of the Company are not considered probable of being achieved. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. The transaction price is then allocated to each performance obligation on a relative standalone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, the Company re-evaluates the probability of achievement of such milestones, and if necessary, adjusts its estimate of the overall transaction price.

Revenue was as follows for the years ended December 31, 2023, 2022 and 2021:

	Year Ended December 31,		
	2023	2022	2021
Neurocrine Biosciences:			
Recognition of the transaction price	$ —	$ 372	$ 3,715
Research and development services	—	1,938	6,452
Milestone payments	—	7,124	5,270
Pacira BioSciences:			
Milestone payments	—	—	3,000
Total revenue	$ —	$ 9,434	$ 18,437

(a) Neurocrine Biosciences license and collaboration agreement:

In December 2019, the Company entered into the Neurocrine Collaboration Agreement with Neurocrine Biosciences. Pursuant to this agreement, the Company granted an exclusive license to XEN901, now known as NBI-921352, and an exclusive license to certain pre-clinical compounds for development (the "DTCs"). The agreement also includes a two-year research collaboration to discover, identify and develop additional novel Nav1.6 and Nav1.2/1.6 inhibitors ("Research Compounds"). The Company and Neurocrine Biosciences collaborated on the conduct of two collaboration programs: (a) a joint research collaboration to discover, identify and preclinically develop Research Compounds (the "Research Program"), which was completed in June 2022, and (b) a collaborative development program for NBI-921352 and two DTCs selected by the joint steering committee (the "Initial Development Program").

At execution of the agreement, Neurocrine Biosciences paid the Company an upfront fee of $50,000, which included a $30,000 payment in cash and a $20,000 equity investment in the Company.

The Company is eligible to receive pre-commercial and commercial milestone payments with respect to the licensed products totaling up to an additional $1,667,500, comprised of up to $1,067,500 in additional development and regulatory milestone payments related to NBI-921352 and other licensed Nav1.6 or Nav1.2/1.6 inhibitor products, and up to $600,000 in additional sales-based milestone payments for multiple products. In addition, the Company is eligible to receive royalties on net sales in and outside the U.S., ranging from (a) for NBI-921352, a low double-digit percentage to a mid-teen percentage and a high-single digit percentage to low double-digit percentage, respectively; (b) for DTCs, a high-single digit percentage to a low double-digit percentage and a mid-single digit percentage to a high-single digit percentage, respectively; and (c) for Research Compounds, a mid-single digit percentage to a high-single digit percentage and a tiered mid-single digit percentage, respectively. Royalty rates are subject to customary reductions.

The Company has an option to co-fund 50% of the development costs of NBI-921352 or another product candidate in the U.S., exercisable upon achievement of certain milestones, in exchange for increased U.S. royalties. The Company has not exercised this option as of December 31, 2023.

The agreement includes the following performance obligations: (i) an exclusive license to NBI-921352 with associated technology and know-how transfer, (ii) an exclusive license to the DTCs with associated know-how transfer, (iii) a license to Research Compounds and research services under the Research Program, (iv) development services under the Initial Development Program for NBI-921352, and (v) development services under the Initial Development Program for the DTCs. The license to the Research Compounds and the research services under the Research Program were considered a single performance obligation as Neurocrine Biosciences cannot benefit from such a license on its own or from other resources commonly available in the industry, without the corresponding research services due to the unique and specialized expertise of the Company that is not readily available in the marketplace. Given the early development phase of the Research Compounds, the performance obligation and related revenue was linked entirely to the performance of research services.

At execution of the agreement, the transaction price consisted of the $30,000 upfront consideration received in cash and a premium of $3,333 on the $20,000 equity investment in the Company measured at fair value on the date of issuance. Under the arrangement, the Company was entitled to funding for certain full-time equivalent and external costs incurred by the Company under performance obligations (iii) and (iv). The arrangement consideration related to the services under performance obligations (iii) and (iv) to be performed on behalf of Neurocrine Biosciences were excluded from the initial transaction price allocation because the consideration and performance were contingent upon Neurocrine Biosciences requesting performance of the services and these services were priced at estimated fair value.

The total transaction price of $33,333 was allocated to performance obligation (v) based on its estimated standalone selling price determined based on internal development plans and budget, with the balance allocated to performance obligations (i) and (ii) by the residual approach. The residual approach was used as standalone selling prices, including market data, for equivalent performance obligations were not available. The allocation of the transaction price requires significant management judgment. The Company allocated the transaction price as follows: $28,807 to performance obligations (i) and (ii) which were delivered and transferred concurrently and completed as of December 2020, and $5,025, which includes $499 of variable consideration, to performance obligation (v), which was completed as of March 2022. The Company measured proportional performance over time using an input method based on cost incurred relative to the total estimated costs for each of the identified obligations at each reporting period. Any changes to estimates were recognized in the period in which they changed as a cumulative catch up.

In September 2021, based on the regulatory approval of a clinical trial application in Europe for NBI-921352 for focal-onset seizures in adults, the Company received an aggregate milestone payment of $10,000 in the form of $4,500 in cash and a $5,500 equity investment in the Company (note 10a). The equity investment was measured at fair value of $4,730 on the date of issuance and the resulting premium of $770, with the cash payment of $4,500, was recognized as revenue in the period as the Company did not have any remaining performance obligations in relation to this milestone on the date it was achieved.

In January 2022, based on the receipt of the U.S. Food and Drug Administration's ("FDA") full IND acceptance for NBI-921352, the Company received an aggregate milestone payment of $15,000 in the form of $6,750 in cash and a $8,250 equity investment in the Company (note 10a). The equity investment was measured at fair value of $7,876 on the date of issuance and the resulting premium of $374, with the cash payment of $6,750, was recognized as revenue in the period as the Company did not have any remaining performance obligations in relation to this milestone on the date it was achieved.

During the years ended December 31, 2022 and 2021, the Company recognized revenue of $2,310 and $10,167, respectively, which comprised of $1,938 and $6,452, respectively, for the research and development services under (iii) the Research Program and (iv) the Initial Development Program for NBI-921352 and $372 and $3,715, respectively, for (v) development services under the Initial Development Program for the DTCs.

(b) Asset Purchase Agreement with Flexion Therapeutics, Inc., subsequently acquired by Pacira BioSciences:

In September 2019, the Company entered into an agreement with Flexion Therapeutics Inc. ("Flexion"), which was acquired by Pacira BioSciences in November 2021, pursuant to which Flexion acquired all rights with respect to XEN402, and a related compound (collectively "XEN402"), including certain regulatory documentation, intellectual property rights, reports, data and all quantities of XEN402, known as PCRX-301, owned or controlled by the Company.

During the year ended December 31, 2021, the FDA cleared the first investigational new drug application for PCRX-301 and a Phase 1b clinical trial was initiated, resulting in milestone payments of $1,000 and $2,000 paid to the Company, respectively. In November 2022, Pacira BioSciences made the strategic decision to no longer pursue the clinical development of PCRX-301.

12. Commitments and contingencies:

(a) Asset purchase agreement with 1st Order Pharmaceuticals, Inc. ("1st Order"):

In April 2017, the Company acquired XEN1101 (previously known as 1OP2198) from 1st Order pursuant to an asset purchase agreement. In August 2020, the Company and 1st Order amended the asset purchase agreement to amend certain definitions in the agreement and to modify the payment schedule for certain milestones. Through December 31, 2023, the Company has paid $2,000 based on progress against these milestones. Future potential payments to 1st Order related to the XEN1101 program include up to $6,000 in regulatory milestones. There are no royalty obligations to 1st Order.

(b) Guarantees and indemnifications:

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

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

13. Income taxes:

Income tax recovery varies from the amounts that would be computed by applying the expected Canadian federal and provincial statutory income tax rate of 27% (2022 and 2021 – 27%) to loss before income taxes as shown in the following table:

	Year Ended December 31,		
	2023	2022	2021
Computed recoveries at Canadian federal and provincial tax rates	$ (49,325)	$ (33,819)	$ (21,300)
Change in valuation allowance	43,829	30,732	21,354
Tax credits earned	(2,868)	(3,086)	(2,279)
Tax attributes expired/utilized	1,442	1,564	692
Non-deductible expenditures	6,482	4,463	2,033
Other	148	264	(506)
Income tax expense (recovery)	$ (292)	$ 118	$ (6)

Income tax expense (recovery) for the years ended December 31, 2023, 2022 and 2021 arose from the operations of Xenon Pharmaceuticals USA Inc., the Company's wholly-owned subsidiary in the United States.

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

	December 31,		
	2023	2022	2021
Scientific research and experimental development pool	$ 38,590	$ 34,891	$ 32,505
Tax credits	30,695	28,835	27,365
Non-capital losses	119,765	80,547	53,453
Depreciable assets	10,311	8,912	7,667
Deferred financing fees	10,831	8,928	7,252
Stock based compensation	3,832	1,492	585
Other	1,220	1,569	732
Less - valuation allowance	(214,442)	(164,665)	(129,094)
Net deferred income tax assets	$ 802	$ 509	$ 465

The realization of deferred income tax assets is dependent upon the generation of sufficient taxable income during future periods in which the temporary differences are expected to reverse. The valuation allowance is reviewed on a quarterly basis and if the assessment of the "more likely than not" criteria changes, the valuation allowance is adjusted accordingly. A full valuation allowance continues to be applied against deferred income tax assets in Canada as the Company has assessed that the realization of such assets does not meet the "more likely than not" criteria. Deferred income tax assets recorded on the consolidated balance sheets as of December 31, 2023 and 2022, result from the temporary differences between the amounts of assets and liabilities recognized for financial statement and income tax purposes, net of valuation allowance, related to the operations of Xenon Pharmaceuticals USA Inc.

At December 31, 2023, the Company has unclaimed tax deductions for scientific research and experimental development expenditures of $142,925 (2022 – $129,226) with no expiry.

At December 31, 2023, the Company has $29,074 (2022 – $27,323) of investment tax credits available to offset federal taxes payable and $8,099 (2022 – $8,418) of provincial tax credits available to offset provincial taxes payable in the future.

At December 31, 2023, the Company has non-capital losses, net of uncertain tax positions, carried forward for tax purposes, which are available to reduce taxable income of future years of approximately $422,822 (2022 – $295,828).

The investment tax credits and loss carry forwards expire over various years to 2043.

At December 31, 2023, the total amount of the Company's unrecognized tax benefits of uncertain tax positions were $10,850 (2022 – $10,850). If recognized in future periods, the unrecognized tax benefits would not affect the Company's effective tax rate. The Company recognizes potential accrued interest and penalties related to unrecognized tax benefits within the income tax provision. Interest and penalties have not been accrued at December 31, 2023 and 2022 as none would be owing on the unrecognized tax benefits due to the availability of non-capital losses to shelter any potential taxable income arising thereon. The Company does not currently expect any significant increases or decreases to these unrecognized tax benefits within 12 months of the reporting date.

The Company files income tax returns in Canada and the United States, the jurisdictions in which the Company believes that it is subject to tax. In jurisdictions in which the Company does not believe it is subject to tax and therefore does not file income tax returns, the Company can provide no certainty that tax authorities in those jurisdictions will not subject one or more tax years (since the inception of the Company) to examination. Further, while the statute of limitations in each jurisdiction where an income tax return has been filed generally limits the examination period, as a result of loss carry-forwards, the limitation period for examination generally does not expire until several years after the loss carry-forwards are utilized. Other than routine audits by tax authorities for tax credits and tax refunds that the Company claims, the Company is not aware of any other material income tax examination currently in progress by any taxing jurisdiction. Tax years ranging from 2003 to 2022 remain subject to examinations in Canada and the United States.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of disclosure controls and procedures. Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2023. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure.

Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2023, our Chief Executive Officer and our Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were, in design and operation, effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting. Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer, is responsible for establishing and maintaining adequate internal control over our financial reporting, as such term is defined in Rule 13a-15(f) and Rule 15d-15(f) of the Securities Exchange Act of 1934. Our internal control over financial reporting is a process to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Our internal control over financial reporting includes those policies and procedures that:

(i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets;

(ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and

(iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

The effectiveness of any system of internal control over financial reporting, including ours, is subject to inherent limitations, including the exercise of judgment in designing, implementing, operating, and evaluating the controls and procedures, and the inability to eliminate misconduct completely. Accordingly, any system of internal control over financial reporting, including ours, no matter how well designed and operated, can only provide reasonable, not absolute, assurances. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions or that the degree of compliance with the policies or procedures may deteriorate. Management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2023. In making its assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control – Integrated Framework (2013) to evaluate the effectiveness of our internal control over financial reporting. Based on this assessment using those criteria, management has concluded that our internal control over financial reporting was effective as of December 31, 2023.

Attestation Report of Independent Registered Public Accounting Firm. The effectiveness of our internal control over financial reporting as of December 31, 2023 has been audited by KPMG LLP, an independent registered public accounting firm, as stated in their report included elsewhere in this Annual Report on Form 10-K.

Changes in internal control over financial reporting. There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the three months ended December 31, 2023 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

We have a written code of conduct that applies to all of our directors, officers and employees. A copy of the most up-to-date version of our code of conduct is available within the "Investors" section on our company website located at http://www.xenon-pharma.com and on SEDAR at www.sedar.com. We will post amendments to our code of conduct or waivers of the same for directors and executive officers on the "Investors" section on our website located at https://www.xenon-pharma.com.

During the three months ended December 31, 2023, no director or Section 16 officer adopted or terminated any Rule 10b5-1 trading arrangements or non-Rule 10b5-1 trading arrangements (in each case, as defined in Item 408(a) of Regulation S-K).

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by Item 10 of Form 10-K is incorporated by reference to our Proxy Statement for the 2024 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2023.

Item 11. Executive Compensation

The information required by Item 11 of Form 10-K is incorporated by reference to our Proxy Statement for the 2024 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2023.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Shareholder Matters

The information required by Item 12 of Form 10-K is incorporated by reference to our Proxy Statement for the 2024 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2023.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by Item 13 of Form 10-K is incorporated by reference to our Proxy Statement for the 2024 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2023.

Item 14. Principal Accounting Fees and Services

The information required by Item 14 of Form 10-K is incorporated by reference to our Proxy Statement for the 2024 Annual Meeting of Shareholders to be filed with the SEC within 120 days after the end of the fiscal year ended December 31, 2023.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Financial Statements — The financial statements included in Item 8 are filed as part of this Annual Report on Form 10-K.

(a)(2) Financial Statement Schedules — All schedules have been omitted because they are not applicable or required, or the information required to be set forth therein is included in the consolidated Financial Statements or notes thereto included in Item 8 of this Annual Report on Form 10-K.

(a)(3) Exhibits — The exhibits required by Item 601 of Regulation S-K are listed in paragraph (b) below.

(b) Exhibits — The exhibits listed in the table below are filed herewith or are incorporated by reference to exhibits previously filed with the SEC.

Exhibit Number	Description of Document	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
3.1	Articles of the Company.	10-Q	001-36687	3.1	December 15, 2014
3.1A	Articles of Amendment to the Articles of the Company, creating the Series 1 Preferred Shares.	8-K	001-36687	3.1	March 28, 2018
3.2	Amended and Restated By-laws of the Company.	10-Q	001-36687	3.2	December 15, 2014
4.1	Form of Common Share Certificate.	S-1/A	333-198666	4.1	October 6, 2014
4.2	Warrant to Purchase Shares, dated August 3, 2018, by and between Xenon Pharmaceuticals Inc. and Silicon Valley Bank.	8-K	001-36687	4.1	August 7, 2018
4.3	Description of Securities.				
4.4	Form of Pre-Funded Warrant.	8-K	001-36687	4.1	October 6, 2021
4.5	Form of Pre-Funded Warrant.	8-K	001-36687	4.1	June 23, 2022
4.6	Form of Pre-Funded Warrant.	8-K	001-36687	4.1	November 30, 2023
10.1#	Stock Option Plan, as amended, and form of option agreement thereunder.	S-1/A	333-198666	10.7	October 6, 2014
10.2#	Amended and Restated 2014 Equity Incentive Plan and form of share option agreement used thereunder.	8-K	001-36687	10.1	June 2, 2022
10.3#	Form of Director and Executive Officer Indemnification Agreement.	S-1/A	333-198666	10.15	October 6, 2014
10.4†	Asset Purchase Agreement, dated April 25, 2017, by and between the Company and 1st Order Pharmaceuticals, Inc.	10-Q	001-36687	10.2	August 3, 2017
10.5	Milestone and Royalty Buy-Out Agreement, dated September 7, 2018, by and among Xenon Pharmaceuticals Inc., Valeant Pharmaceuticals Ireland Limited and Valeant Pharmaceuticals Luxembourg S.a.r.l.	8-K	001-36687	10.1	September 11, 2018
10.6#	Amended and Restated Employment Agreement, dated March 19, 2019, by and between the Company and Robin Sherrington.	10-K	001-36687	10.24	March 9, 2020
10.7#	Employment Agreement, dated July 17, 2020, by and between the Company and Christopher Von Seggern.	10-Q	001-36687	10.3	November 5, 2020
10.8#	Employment Agreement, dated January 13, 2021, by and between the Company and Ian Mortimer.	8-K	001-36687	10.2	January 14, 2021
10.9#	Employment Agreement, dated January 13, 2021, by and between the Company and Sherry Aulin.	8-K	001-36687	10.4	January 14, 2021

Exhibit Number	Description of Document	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
10.10#	Employment Agreement, dated August 18, 2021, by and between the Company and Christopher Kenney.	10-Q	001-36687	10.3	November 10, 2021
10.11#	2019 Inducement Equity Incentive Plan and related form of share option agreement.	8-K	001-36687	10.1	September 10, 2019
10.12††	License and Collaboration Agreement, dated as of December 2, 2019, by and between Xenon Pharmaceuticals Inc. and Neurocrine Biosciences, Inc.	8-K	001-36687	10.1	December 2, 2019
10.13	Share Purchase Agreement, dated as of December 2, 2019, by and between Xenon Pharmaceuticals Inc. and Neurocrine Biosciences, Inc.	8-K	001-36687	10.2	December 2, 2019
10.14††	Amendment No. 1 to Asset Purchase Agreement, dated August 4, 2020, by and between the Company and 1st Order Pharmaceuticals Inc.	10-Q	001-36687	10.2	August 6, 2020
10.15	At-the-Market Equity Offering Sales Agreement dated as of August 6, 2020, by and among Xenon Pharmaceuticals Inc., Jefferies LLC and Stifel, Nicolaus & Company, Incorporated.	8-K	001-36687	1.1	August 6, 2020
10.16	Amendment No. 1 to the At-the-Market Equity Offering Sales Agreement, dated March 1, 2022, by and among Xenon Pharmaceuticals Inc., Jefferies LLC and Stifel, Nicolaus & Company, Incorporated.	8-K	001-36687	1.1	March 1, 2022
10.17††	Amendment #1, dated January 13, 2021, to the License and Collaboration Agreement, dated December 2, 2019, by and between Xenon Pharmaceuticals Inc. and Neurocrine Biosciences, Inc.	8-K	001-36687	10.1	January 14, 2021
10.18	Termination Agreement, dated August 6, 2021, by and among Xenon Pharmaceuticals Inc., Genentech, Inc. and F. Hoffmann-La Roche Ltd.	10-Q	001-36687	10.1	August 11, 2021
10.19	Share Purchase Agreement, dated as of September 8, 2021, by and between Xenon Pharmaceuticals Inc. and Neurocrine Biosciences, Inc.	8-K	001-36687	10.1	September 8, 2021
10.20	Lease Agreement, effective November 24, 2021, by and between the Company and Redstone Enterprises Ltd.	8-K	001-36687	10.1	December 1, 2021
10.21	Share Purchase Agreement, dated as of January 11, 2022, by and between Xenon Pharmaceuticals Inc. and Neurocrine Biosciences, Inc.	8-K	001-36687	10.1	January 12, 2022
10.22††	Amendment #2, dated February 25, 2022, to the License and Collaboration Agreement, dated December 2, 2019, by and between Xenon Pharmaceuticals Inc. and Neurocrine Biosciences, Inc.	10-K	001-36687	10.30	March 1, 2022
10.23††	Consent to Alterations and Lease Modification Agreement between Redstone Enterprises Ltd. and Xenon Pharmaceuticals Inc., effective May 19, 2022.	10-Q	001-36687	10.1	August 9, 2022
10.24#	Employment Agreement, dated November 7, 2022, by and between the Company and Andrea DiFabio.	10-Q	001-36687	10.1	November 8, 2022
10.25#	Executive Incentive Compensation Plan.	8-K	001-36687	10.1	March 14, 2023

Exhibit Number	Description of Document	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
10.26	Consent to Alterations Agreement between Redstone Enterprises Ltd. and Xenon Pharmaceuticals Inc., effective March 27, 2023.	10-Q	001-36687	10.1	August 9, 2023
10.27	Consent to Alterations Agreement between Redstone Enterprises Ltd. and Xenon Pharmaceuticals Inc., effective August 16, 2023.				
10.28#	Employment Agreement, dated December 15, 2023, by and between the Company and James Empfield.				
21.1	List of Subsidiaries of the Company.	10-K	001-36687	21.1	March 8, 2017
23.1	Consent of KPMG LLP, Independent Registered Public Accounting Firm.				
24.1	Powers of Attorney (contained on signature page).				
31.1	Rule 13a-14(a) / 15d-14(a) Certification of Principal Executive Officer				
31.2	Rule 13a-14(a) / 15d-14(a) Certification of Principal Financial Officer				
32.1*	Section 1350 Certification of Principal Executive Officer				
32.2*	Section 1350 Certification of Principal Financial Officer				
97	Clawback Policy, effective as of October 2, 2023				
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document				
101.SCH	Inline XBRL Taxonomy Extension Schema Document with Embedded Linkbases Document				
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)				

† Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

†† Portions of this exhibit have been omitted in accordance with Item 601(b)(10) of Regulation S-K because they are private, confidential and not material.

# Indicates management contract or compensatory plan.

* The Certifications attached as Exhibits 32.1 and 32.2 that accompany this Annual Report on Form 10-K are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of Xenon Pharmaceuticals Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Dated: February 29, 2024

XENON PHARMACEUTICALS INC.

By: /s/ Ian Mortimer
Ian Mortimer
President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose signature appears below hereby constitutes and appoints Simon Pimstone, Ian Mortimer and Sherry Aulin, and each of them severally, as his or her true and lawful attorneys-in-fact and agents, with full power to act without the other and with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities (including his or her capacity as a director and/or officer of Xenon Pharmaceuticals Inc.) to sign any and all amendments and supplements to this report, and any and all other instruments necessary or incidental in connection herewith, and to file the same, with all exhibits thereto, and all other documents in connection therewith, with the Commission.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Ian Mortimer Ian Mortimer	President, Chief Executive Officer and Director (Principal Executive Officer)	February 29, 2024
/s/ Sherry Aulin Sherry Aulin	Chief Financial Officer (Principal Financial and Accounting Officer)	February 29, 2024
/s/ Simon Pimstone Simon Pimstone	Chair of the Board of Directors	February 29, 2024
/s/ Mohammad Azab Mohammad Azab	Director	February 29, 2024
/s/ Gillian Cannon Gillian Cannon	Director	February 29, 2024
/s/ Steven Gannon Steven Gannon	Director	February 29, 2024
/s/ Elizabeth Garofalo Elizabeth Garofalo	Director	February 29, 2024
/s/ Justin Gover Justin Gover	Director	February 29, 2024
/s/ Patrick Machado Patrick Machado	Director	February 29, 2024
/s/ Gary Patou Gary Patou	Director	February 29, 2024
/s/ Dawn Svoronos Dawn Svoronos	Director	February 29, 2024