Xenon Pharmaceuticals Inc.
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Registration No. 333-208376

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and they are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED SEPTEMBER 12, 2018

PRELIMINARY PROSPECTUS SUPPLEMENT

(To Prospectus Dated January 5, 2016)

Shares

Common Shares

We are offering of our common shares. Our common shares are listed on The Nasdaq Global Market under the symbol "XENE." The last reported sale price of our common shares on The Nasdaq Global Market on September 11, 2018 was $14.90 per share.

Investing in our common shares involves a high degree of risk. See "Risk Factors" beginning on page S 5 of this prospectus supplement and under similar headings in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

We are an "emerging growth company" under applicable Securities and Exchange Commission rules and are eligible for reduced public company disclosure requirements.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Per Common Share	Total
Public Offering Price	$	$

Underwriting Discounts and Commissions [(1)]	$	$
Proceeds to Xenon Pharmaceuticals Inc., before expenses	$	$

(1) See "Underwriting" beginning on page S-53 of this prospectus supplement for additional information regarding underwriters' compensation.

Delivery of the common shares is expected to be made on or about September , 2018. We expect to grant the underwriters an option for a period of 30 days to purchase up to an additional common shares. If the underwriters exercise the option in full, the total underwriting discounts and commissions will be $, and the total proceeds to us, before expenses, will be $.

Joint Book-Running Managers

Jefferies Stifel

Prospectus Supplement dated September , 2018

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus dated January 5, 2016 form part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission (SEC), utilizing a "shelf" registration process. This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common share offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus supplement, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date-for example, a document incorporated by reference in the accompanying prospectus-the statement in the document having the later date modifies or supersedes the earlier statement.

Neither we nor the underwriters have authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus or any free writing prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus or any free writing prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein or therein or any free writing prospectus is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any free writing prospectus or of any sale of our common shares. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein or any free writing prospectus, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled "Where You Can Find More Information" and "Information Incorporated by Reference" in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, common shares only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus or any free writing prospectus and the offering of the common shares in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus or any free writing prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common shares and the distribution of this prospectus supplement and the accompanying prospectus or any free writing prospectus outside the United States.

Unless the context requires otherwise, references in this prospectus supplement to "Xenon," "the Company," "we," "us" and "our" refer to Xenon Pharmaceuticals Inc. and its subsidiary.

PROSPECTUS SUPPLEMENT SUMMARY

This summary description about us and our business highlights selected information contained elsewhere in this prospectus supplement or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all of the information that you should consider before deciding to invest in our common shares. You should carefully read this entire prospectus supplement, the accompanying prospectus and any related free writing prospectus, including each of the documents incorporated herein or therein by reference, before making an investment decision. Investors should carefully consider the information set forth under "Risk Factors" in this prospectus supplement beginning on page S-5 and in any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus supplement and the accompanying prospectus. You also should carefully read the information incorporated by reference into this prospectus supplement and the accompanying prospectus, including our financial statements, other information and the exhibits to the registration statement of which the accompanying prospectus is a part.

Overview

We are a clinical stage, neurology-focused biopharmaceutical company focused on developing innovative therapeutics to improve the lives of patients with neurological disorders. To date, our pharmaceutical collaborations have generated in aggregate over $160.0 million in non-equity funding with the potential to provide us with future milestone payments, as well as royalties on product sales. Our current pharmaceutical partners include Genentech, Inc., or Genentech, a member of the Roche Group, and Merck & Co., Inc., or Merck (through its affiliate, Essex Chemie AG).

Building upon our extensive knowledge of human genetics and diseases caused by mutations in ion channels, known as channelopathies, we are advancing a novel product pipeline of central nervous system, or CNS, therapies to address areas of high unmet medical need, such as epilepsy, migraine and pain.

XEN496 for the Treatment of Epilepsy

XEN496 (active ingredient ezogabine – an anti-epileptic drug previously approved by the FDA) is a Kv7 potassium channel modulator for the potential treatment of epilepsy. Based on feedback from the U.S. Food and Drug Administration, or FDA, we anticipate initiating a single, pivotal Phase 3 clinical trial examining XEN496's efficacy as a treatment of KCNQ2 epileptic encephalopathy, or KCNQ2-EE, also known as EIEE7. We believe published case reports where physicians have used ezogabine in infants and young children with KCNQ2-EE indicate that XEN496 may be efficacious in this often hard-to-treat pediatric patient population. We have received orphan drug designation, or ODD, from the FDA for XEN496 as a treatment of KCNQ2-EE and are currently working on a pediatric-specific formulation for XEN496 to support a Phase 3 clinical trial initiation in approximately mid-2019. KCNQ2-EE is rare, representing around 10% of patients with epileptic encephalopathy with onset in the first three months of life; we estimate that the incidence of KCNQ2-EE based on published literature is approximately 2.8/100,000 live births, which is roughly half the number of births of Dravet Syndrome, the most common genetic cause of early infantile epileptic encephalopathy.

XEN1101 for the Treatment of Epilepsy

XEN1101 is a Kv7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders. We have now completed enrollment in the XEN1101 Phase 1 clinical trial using a powder-in-capsule formulation, which is evaluating the safety, tolerability and pharmacokinetics of both single ascending doses, or SAD, and multiple ascending doses, or MAD, of XEN1101. We have disclosed data from the completed XEN1101 Phase 1b transcranial magnetic stimulation, or TMS, study that demonstrated XEN1101 has an ability to inhibit cortical excitability, an important CNS effect observed with certain approved anti-epileptic drugs, or AEDs. We plan to publish the complete XEN1101 Phase 1 clinical trial results at an upcoming scientific meeting and anticipate initiating a Phase 2 clinical trial evaluating XEN1101 as a treatment for adult focal seizures in the fourth

quarter of 2018.

XEN901 for the Treatment of Epilepsy

XEN901 is a potent, highly selective Nav1.6 sodium channel inhibitor being developed for the treatment of epilepsy. A randomized, double-blind, placebo-controlled Phase 1 clinical trial to evaluate XEN901's safety, tolerability and pharmacokinetics in both SAD and MAD cohorts is ongoing. A read-out of the final results is anticipated in the fourth quarter of 2018 and we expect to initiate a Phase 2 clinical trial as soon as feasible thereafter to evaluate XEN901's efficacy as a treatment for adult focal seizures or for rare, pediatric forms of epilepsy depending on planned discussions with regulatory agencies.

XEN007 for the Treatment of Hemiplegic Migraine

XEN007 (active ingredient flunarizine) is a CNS-acting calcium channel inhibitor that directly modulates Cav2.1, which is a critical calcium channel implicated in the pathophysiology of hemiplegic migraine, or HM, a rare and debilitating neurological disorder. Flunarizine has been used outside of the U.S. in the prevention of chronic migraine and has been reported to have clinical benefit in HM case studies. We have received ODD for XEN007 for the treatment of HM. We have entered into key agreements in order to access regulatory files and manufacturing support to potentially enable the accelerated clinical development of XEN007 directly into a Phase 2 clinical trial. We are currently evaluating various development strategies for XEN007, including the support of physician-sponsored clinical trials.

Selective Inhibitors of Nav1.7 for the Treatment of Pain

We have an ongoing collaboration with Genentech focused on developing novel inhibitors of Nav1.7 for the treatment of pain. Genentech has completed a Phase 1 clinical trial for GDC-0310, which is an oral, selective Nav1.7 small-molecule inhibitor developed for the potential treatment of pain. Guidance around the future clinical development of GDC-0310 will be updated once ongoing pre-clinical studies are completed and the final results are analyzed by Genentech.

Recent Developments

On September 10, 2018, we signed an agreement with Valeant Pharmaceuticals Luxembourg S.a.r.l. and Valeant Pharmaceuticals Ireland Limited to buy out all milestone payments and royalties 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.

On September 12, 2018, in connection with this offering, we suspended the offering of, and during the duration of this offering we are no longer offering, any securities pursuant to the prospectus supplement filed with the SEC on July 12, 2018 relating to the offer and sale of our common shares pursuant to the at-the-market equity offering sales agreement dated July 11, 2018 among us, Jefferies LLC and Stifel, Nicolaus & Company, Incorporated.

Financial Information

As of June 30, 2018, we had $63.3 million of cash and cash equivalents and marketable securities and an accumulated deficit of $184.9 million.

About Xenon

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, on May 17, 2000 and concurrently changed our name to “Xenon Genetics Inc.” We registered as an extra-provincial company in British Columbia on July 10, 2000 and changed our name to “Xenon Pharmaceuticals Inc.” on August 24, 2004. We have one wholly-owned subsidiary as of December 31, 2017, Xenon Pharmaceuticals USA Inc., which was incorporated in Delaware on December 2, 2016. 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.”

Our principal executive offices are located at 200 - 3650 Gilmore Way, Burnaby, British Columbia, Canada V5G 4W8, and our telephone number is (604) 484-3300. Our website address is www.xenon-pharma.com. The information contained in, or that can be accessed through, our website is not part of this prospectus supplement.

THE OFFERING

Common shares offered by us	shares (shares if the underwriters' option to purchase additional shares is exercised in full).
Option to purchase additional shares	We expect to grant the underwriters an option to purchase up to additional common shares. This option is exercisable, in whole or in part, for a period of 30 days from the date of this prospectus supplement.
Common shares to be outstanding after this offering	shares (shares if the underwriters' option to purchase additional shares is exercised in full).
Use of proceeds	We estimate that the net proceeds to us from this offering, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, will be approximately $ million, or approximately $ million if the underwriters exercise their option to purchase additional shares from us in full. We currently expect to use the net proceeds to us from this offering for external and personnel-related expenses associated with the ongoing clinical development of our XEN496, XEN1101 and XEN901 product candidates; for external and personnel-related expenses associated with the development of our XEN007 product candidate, which we are currently evaluating to enter into physician-sponsored clinical trials; to fund our ion channel and other discovery activities; and for working capital, capital expenditures and other general corporate purposes. See "Use of Proceeds" on page S-41 of this prospectus supplement.
Risk factors	An investment in our common shares involves a high degree of risk. See "Risk Factors" beginning on page S-5 of this prospectus supplement and the similarly titled sections in the documents incorporated by reference into this prospectus supplement.
Nasdaq Global Market symbol	XENE

Outstanding Shares

The number of common shares to be outstanding after this offering is based on 20,508,951 common shares outstanding as of June 30, 2018, which number includes 2,868,000 common shares issuable upon the conversion of 2,868,000 of our Series 1 Preferred Shares outstanding as of June 30, 2018, and excludes:

- 1,600,000 common shares sold subsequent to June 30, 2018 pursuant to our July 2018 at-the-market equity offering sales agreement with Jefferies LLC and Stifel, Nicolaus & Company, Incorporated;
- 2,831,985 common shares issuable upon the exercise of outstanding options to purchase common shares as of June 30, 2018, at a weighted average exercise price of $6.95 per common share;
- 107,322 common shares reserved for future issuance as of June 30, 2018 under our 2014 Equity Incentive Plan, as amended, and any future automatic increase in common shares reserved for issuance under such plan; and
- 126,419 common shares issuable upon the exercise of warrants outstanding, at a weighted-average exercise price of $4.76 per share.

Except as otherwise indicated herein, all information in this prospectus supplement, including the number of shares that will be outstanding after this offering, assumes no exercise by the underwriters of their option to purchase additional shares.

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RISK FACTORS

Investing in our common shares involves a high degree of risk. You should carefully consider the risks described below, as well as all other information included in this prospectus supplement, the accompanying prospectus and in our other filings with the SEC incorporated by reference into this prospectus supplement before you decide to purchase common shares. If any of the following risks actually occurs, our business, financial condition, operating results, prospects and ability to accomplish our strategic objectives could be materially harmed. As a result, the trading price of our common shares could decline and you could lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations and the market price of our common shares.

Risks Related to Our Financial Condition and Capital Requirements

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

We are a clinical stage biotechnology company and, other than the years ended December 31, 2014 and 2013, we have recorded net losses in each annual reporting period since inception in 1996, and we do not expect to have sustained profitability for the foreseeable future. We had net losses of $11.6 million for the six months ended June 30, 2018 and an accumulated deficit of $184.9 million as of June 30, 2018, which were driven by expenses incurred in connection with our research and development programs and from general and administrative costs associated with our operations.

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

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

- continue our research and pre-clinical and clinical development of our product candidates;
- expand the scope of our clinical studies for our current and prospective product candidates;
- initiate additional pre-clinical, clinical or other studies for our product candidates;
- change or add additional manufacturers or suppliers;
- seek regulatory and marketing approvals for any of our product candidates that successfully complete clinical studies;
- seek to identify and validate additional product candidates;
- acquire or in-license other product candidates and technologies;
- make milestone or other payments under our in-license or other agreements, including, without limitation, payments to Memorial University of Newfoundland, 1st Order Pharmaceuticals, Inc. and other third parties;
- maintain, protect and expand our intellectual property portfolio;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- create additional infrastructure to support our operations and our product development and planned future commercialization efforts; and
- experience any delays or encounter issues with any of the above.

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

We have not generated any significant royalty revenue from product sales and may never become profitable on a U.S. GAAP basis.

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

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

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

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

Since our inception, we have dedicated most of our resources to the discovery and development of our proprietary pre-clinical and clinical product candidates, and we expect to continue to expend substantial resources doing so for the foreseeable future. These expenditures will include costs associated with research and development, potential milestone payments to third parties, manufacturing of product candidates and products approved for sale, conducting pre-clinical experiments and clinical trials and obtaining and maintaining regulatory approvals, as well as commercializing any products later approved for sale. During the six months ended June 30, 2018, we incurred approximately $11.0 million of costs associated with research and development, exclusive of costs incurred by our collaborators in developing our product candidates.

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

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

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

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

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

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

In December 2017, we entered into a loan and security agreement with Silicon Valley Bank pursuant to which we borrowed an aggregate principal amount of $12.0 million up to June 30, 2018. In August 2018, we entered into an amended and restated loan and security agreement with Silicon Valley Bank providing for a term loan to us with an aggregate principal amount of $15.5 million, which amount was funded in August 2018. Proceeds from the principal amount borrowed in August 2018 will be used in part to refinance the amounts borrowed under the December 2017 loan and security agreement and pay a $0.5 million final payment fee to Silicon Valley Bank in connection with the refinancing of the December 2017 loan and security agreement.

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

- sell, transfer or otherwise dispose of any of our business assets or property, subject to limited exceptions;
- make material changes to our business;

- enter into transactions resulting in significant changes to the voting control of our stock;
- make certain changes to our organizational structure;