

The information in this preliminary prospectus supplement is not complete and may be changed. This preliminary prospectus supplement and the accompanying prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED MAY 31, 2023

PRELIMINARY PROSPECTUS SUPPLEMENT

(To Prospectus Dated September 14, 2021)



Shares

Lexicon Pharmaceuticals, Inc.

Common Stock
\$ per share

We are selling an aggregate of _____ shares of our common stock, par value \$0.001 per share.

We have granted the underwriters an option to purchase up to an aggregate of _____ additional shares of our common stock.

An affiliate (the "Private Placement Purchaser") of Invus, L.P., our largest stockholder, is purchasing an aggregate of _____ shares of our common stock in a concurrent private placement (the "Concurrent Private Placement") exempt from the registration requirements of the Securities Act of 1933, as amended (the "Securities Act"), at the same price as the price to the public in this offering for aggregate gross proceeds of \$ _____ million pursuant to a preemptive right contained in our Fifth Amended and Restated Certificate of Incorporation (the "Certificate of Incorporation"). The Concurrent Private Placement is contingent on the closing of this offering and the satisfaction of certain other customary conditions. If, and to the extent, the underwriters exercise their option to purchase additional shares, the Private Placement Purchaser will have the option to purchase a proportionate amount of additional shares pursuant to its preemptive right in an additional closing of the Concurrent Private Placement. See "Concurrent Private Placement" and "Underwriting" beginning on pages S-12 and S-13, respectively.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "LXRX." The last reported sale price of our common stock on the Nasdaq Global Select Market on May 30, 2023 was \$2.90 per share.

Investing in our common stock involves risks. See "[Risk Factors](#)" beginning on page S-5 of this prospectus supplement and in the section titled "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2022, as updated by our subsequent Quarterly Report on Form 10-Q, which are incorporated by reference into this prospectus supplement and the accompanying prospectus.

Neither the Securities and Exchange Commission (the "SEC") 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 Share	Total
Public Offering Price	\$	\$
Underwriting Discounts and Commissions ⁽¹⁾	\$	\$
Proceeds to Lexicon Pharmaceuticals, Inc. (before expenses)	\$	\$

(1) In addition, we have agreed to reimburse the underwriters for certain of their expenses. See "Underwriting" for additional disclosure regarding the underwriting discounts and commissions and estimated offering expenses.

The underwriters expect to deliver the shares of our common stock to purchasers on or about _____, 2023 through the book-entry facilities of The Depository Trust Company.

Citigroup

Jefferies

Piper Sandler

, 2023

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock 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 dated September 14, 2021, including the documents incorporated by reference therein, provides more general information. Generally, when we refer to this prospectus, 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 herein 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 prospectus supplement modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

You should rely only on the information contained in this prospectus supplement and the accompanying prospectus and the documents incorporated by reference herein. We have not authorized, and the underwriters have not authorized, anyone to provide you with information that is different. The information contained in this prospectus supplement, the accompanying prospectus or the documents incorporated by reference herein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our securities. It is important for you to read and consider all information contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein, 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 “Incorporation of Certain Information by Reference” in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our securities only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of our securities 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 must inform themselves about, and observe any restrictions relating to, the offering of our securities and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Unless otherwise stated, all references in this prospectus to “we,” “us,” “our,” “Lexicon,” the “Company” and similar designations refer to Lexicon Pharmaceuticals, Inc. and its wholly-owned subsidiaries. We own or have rights to trademarks or trade names that we use in connection with the operation of our business. The Lexicon name and logo are registered trademarks of Lexicon Pharmaceuticals, Inc. All other trademarks or service marks appearing in this prospectus supplement are the property of their respective holders.

PROSPECTUS SUPPLEMENT SUMMARY

The following summary highlights selected information contained elsewhere in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein. This summary sets forth the material terms of this offering but does not contain all of the information you should consider before investing in our securities. You should read carefully this entire prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein, before making an investment decision, especially the risks of investing in the securities discussed in the section titled “Risk Factors” in this prospectus supplement as well as the consolidated financial statements and notes to those consolidated financial statements incorporated by reference into this prospectus supplement and the accompanying prospectus. Some of the statements in this prospectus supplement constitute forward-looking statements that involve risks and uncertainties. See “Cautionary Note Regarding Forward-Looking Statements.” Our actual results could differ materially from those anticipated in such forward-looking statements as a result of certain factors, including those discussed in “Risk Factors” in this prospectus supplement, accompanying prospectus and the documents incorporated by reference herein and elsewhere in this prospectus supplement.

Overview and Recent Developments

We are a biopharmaceutical company with a mission of pioneering medicines that transform patients’ lives. On May 26, 2023 the U.S. Food and Drug Administration, or FDA, approved INPEFA™ (sotagliflozin), our once-daily oral tablet to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failures or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors. The approval was supported by positive results from two Phase 3 clinical trials evaluating the effect of INPEFA on long-term outcomes related to cardiovascular death and heart failure in approximately 10,500 and 1,200 patients, respectively. We are now in the process of commercially launching INPEFA in the United States and expect it to be commercially available by the end of June 2023.

We intend for our sales field team to be focused on both high-volume treaters and the top heart failure institutions. Our sales field team is sized to cover a total of approximately 22,000 targeted health care professionals, with a primary focus on a subset of approximately 8,000 health care professionals who are responsible for the greatest proportion of heart failure treatment decisions, and approximately 1,800 targeted heart failure institutions. Selection of these health care professionals was based on the volume of branded heart failure prescriptions and, for institutions, the number of heart failure discharges. To date, our sales field team has booked over 5,000 appointments with health care professionals or within institutions that will begin in June 2023.

Our market access field team is focused on both national and regional commercial and Medicare payers, as well as institutional accounts. Our corporate account directors are focused on generating access in the largest payers in the United States, including five group purchasing organizations, 15 federal government programs, 20 national pharmacy benefit managers and health plans and 64 key regional health plans, while our directors of strategic accounts are focused on generating access in 60 integrated delivery networks, or IDNs, and over 1,900 targeted aligned hospitals.

We have focused our payer access efforts by prioritizing accounts based on the number of heart failure lives, and we have tailored those efforts by deploying unique engagement strategies for the messages we think will resonate most with each class of payer. Our targeted Medicare, IDN and commercial business segments represent approximately 3,200,000, 1,900,000 and 1,300,000 heart failure lives, respectively.

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In addition to our commercial launch of INPEFA, we continue to devote most of our remaining resources to the following research and development initiatives:

- We are preparing for late-stage development of LX9211, an orally-delivered small molecule drug candidate, as a treatment for diabetic peripheral neuropathic pain. We previously reported positive results from a Phase 2 clinical trial of LX9211 in diabetic peripheral neuropathic pain and LX9211 has received Fast Track designation from the FDA for development in that indication.
- We are conducting preclinical research and development and preparing to conduct clinical development of compounds from a number of additional drug programs originating from our internal drug discovery efforts.

INPEFA and compounds from a number of additional drug programs originated from our own internal drug discovery efforts, and LX9211 originated from our collaborative neuroscience drug discovery efforts with Bristol-Myers Squibb. Our efforts were driven by a systematic, target biology-driven approach in which we used gene knockout technologies and an integrated platform of advanced medical technologies to systematically study the physiological and behavioral functions of almost 5,000 genes in mice and assessed the utility of the proteins encoded by the corresponding human genes as potential drug targets. We have identified and validated in living animals, or in vivo, more than 100 targets with promising profiles for drug discovery.

We are working both independently and through collaborations and strategic alliances with third parties to capitalize on our drug target discoveries and drug discovery and development programs. We seek to retain exclusive or co-exclusive rights to the benefits of certain drug discovery and development programs by developing and commercializing drug candidates from those programs internally, particularly in the United States for indications treated by specialist physicians. We seek to collaborate with other pharmaceutical and biotechnology companies with respect to drug discovery or the development and commercialization of certain of our drug candidates, particularly with respect to commercialization in territories outside the United States or commercialization in the United States for indications treated by primary care physicians, or when the collaboration may otherwise provide us with access to expertise and resources that we do not possess internally or are complementary to our own.

Company Information

Our principal executive offices are located at 2445 Technology Forest Blvd., 11th Floor, The Woodlands, Texas 77381. Our telephone number is (281) 863-3000. Our website is located at www.lexpharma.com. Unless indicated otherwise, no information is incorporated herein by reference from our website or any other website and no website constitutes a part of this prospectus supplement. Our common stock is listed on The Nasdaq Global Select Market (“Nasdaq”) under the symbol “LXRX.”

Concurrent Private Placement

The Private Placement Purchaser, an affiliate of Invus, L.P., our largest stockholder, is purchasing an aggregate of _____ shares of our common stock in a concurrent private placement exempt from the registration requirements of the Securities Act, at the same price as the price to the public in this offering for aggregate gross proceeds of \$ _____ million. The underwriters will not receive any underwriting discounts or commissions on any shares of common stock sold to the Private Placement Purchaser or its affiliates. The Concurrent Private Placement is contingent on the closing of this offering and the satisfaction of certain other customary conditions. In connection with the Concurrent Private Placement, we will enter into a securities purchase agreement with the Private Placement Purchaser and certain other affiliates of Invus, L.P.

THE OFFERING

Common stock offered by us	shares of common stock (or shares if the underwriters exercise their option to purchase additional shares of our common stock in full).
Option to purchase additional shares	We have granted the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to an additional shares of our common stock. If this option is exercised, the Private Placement Purchaser will have the option to purchase a proportionate amount of additional shares of our common stock pursuant to its preemptive right in an additional closing of the Concurrent Private Placement.
Concurrent Private Placement	The Private Placement Purchaser, an affiliate of Invus, L.P., our largest stockholder, is purchasing an aggregate of shares of our common stock in a concurrent private placement exempt from the registration requirements of the Securities Act, at the same price as the price to the public in this offering for aggregate gross proceeds of \$ million pursuant to a preemptive right contained in our Certificate of Incorporation. The underwriters will not receive any underwriting discounts or commissions on any shares of common stock sold to the Private Placement Purchaser or its affiliates. The Concurrent Private Placement is contingent on the closing of this offering and the satisfaction of certain other customary conditions.
Common stock to be outstanding immediately after this offering and the Concurrent Private Placement	shares (or shares if the underwriters exercise their option to purchase additional shares of our common stock in full and the Private Placement Purchaser exercises its proportionate preemptive right in full).
Use of proceeds	We estimate that the net proceeds to us from this offering and the Concurrent Private Placement, 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 of our common stock in full and the Private Placement Purchaser exercises its proportionate preemptive right in full. We currently intend to use a portion of the net proceeds from this offering and the Concurrent Private Placement, together with our existing cash and cash equivalents and short-term investments, to (i) fund the commercial launch of INPEFA, and (ii) fund the continued research and development of our drug candidates and for working capital and other general corporate purposes. See “Use of Proceeds.”

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Risk factors See “Risk Factors” beginning on page S-5 and similar sections in the accompanying prospectus and documents incorporated by reference herein for a discussion of certain factors you should carefully consider before deciding to invest in shares of our common stock.

The Nasdaq Global Select Market symbol Our common stock is listed on Nasdaq under the symbol “LXRX.”

The number of shares of our common stock to be outstanding immediately after this offering and the Concurrent Private Placement is based on 189,561,819 shares outstanding as of May 2, 2023, and excludes the following:

- 17,127,000 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2023, with a weighted-average exercise price of \$4.25 per share;
- 5,490,000 shares of common stock issuable upon the vesting of outstanding restricted stock units as of March 31, 2023;
- 420,673 shares of common stock issuable pursuant to outstanding warrants as of March 31, 2023, with a warrant price of \$2.08 per share;
- 224,128 shares of common stock issuable pursuant to outstanding warrants as of March 31, 2023, with a warrant price of \$1.95 per share; and
- 25,224,727 shares of common stock reserved for future issuance under our 2017 Equity Incentive Plan and 2017 Non-Employee Directors’ Equity Incentive Plan, as of March 31, 2023 and after giving effect to the approval by our shareholders of certain additional authorized shares of common stock thereunder on April 27, 2023.

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

RISK FACTORS

An investment in our securities involves risk. You should carefully consider the risk factors set forth in “Item 1A. Risk Factors” of our Annual Report on Form 10-K for the year ended December 31, 2022, and our subsequently filed Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, together with all of the other information included in, or incorporated by reference into, this prospectus supplement and the accompanying base prospectus, when evaluating an investment in our securities. If any of these risks were to occur, our business, financial condition or results of operations could be materially adversely affected. In that case, the trading price of our common stock could decline and you could lose all or part of your investment.

Risks Related to this Offering

Following regulatory approval of INPEFA in the United States, we will now depend heavily on the commercial success of INPEFA in heart failure. If we do not achieve commercial success with INPEFA, our business will suffer and our stock price will likely decline.

Although INPEFA has now received regulatory approval in the United States, we cannot be certain that INPEFA will be commercially successful. We expect that a significant portion of our total revenues will be attributable to sales of INPEFA for heart failure in the United States; however, our future sales of INPEFA will depend on numerous factors, including:

- the number of patients suffering from heart failure;
- competition from dapagliflozin, empagliflozin and, to some extent, other classes of drugs used in the treatment of heart failure, such as the combination drug sacubitril/valsartan;
- the safety profile of INPEFA, including whether previously unknown side effects or increased incidence or severity of known side effects as compared to those seen during development are identified with the commercial use of INPEFA;
- the effectiveness of our commercial strategy for marketing INPEFA and our execution of that strategy, including our pricing strategy and the effectiveness of our efforts to obtain and maintain adequate third-party reimbursement;
- the acceptance of INPEFA by patients, the medical community and third-party payers; and
- our ability to meet the demand for commercial supplies of INPEFA and to maintain and successfully monitor commercial manufacturing arrangements for INPEFA with third-party manufacturers to ensure they meet our standards and those of the FDA, which extensively regulates and monitors pharmaceutical manufacturing facilities.

While we believe that INPEFA has a competitive commercial profile, our current estimates of the revenues that INPEFA could generate in future periods may change based upon the above factors, and could prove to be incorrect. Although we expect to bring INPEFA to market in the United States by the end of June 2023, we may face delays in our commercialization processes, and we cannot make any assurances INPEFA will be commercially available at such time. We plan to set INPEFA’s wholesale acquisition cost comparable to existing branded heart failure medications. If our revenues, market share or other indicators of market acceptance of INPEFA fail to meet the expectations of investors or public market analysts, the market price of our common stock could decline. In addition, if one or more of the factors (including the wholesale acquisition cost of INPEFA) above negatively affects INPEFA sales, our business and financial condition could be materially harmed and we may be more heavily dependent on the success of our other drug programs.

We have broad discretion in the use of the net proceeds from this offering and the Concurrent Private Placement and may not use them effectively.

As of the date of this prospectus supplement, we cannot specify with certainty the particular uses for the net proceeds we will receive from this offering and the Concurrent Private Placement. We will have broad discretion

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in the application of the net proceeds, including any of the purposes described in “Use of Proceeds.” Any failure by us to apply these funds effectively could have a material adverse effect on our business.

Provisions contained in our charter documents and Delaware law may inhibit a takeover attempt, which could reduce or eliminate the likelihood of a change of control transaction and, therefore, the ability of our stockholders to sell their shares for a premium.

Provisions in our corporate charter and bylaws and applicable provisions of the Delaware General Corporation Law may make it more difficult for a third party to acquire control of us without the approval of our board of directors. These provisions include:

- a classified board of directors;
- limitations on the removal of directors;
- limitations on stockholder proposals at meetings of stockholders;
- the inability of stockholders to act by written consent or to call special meetings; and
- the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval.

These provisions may discourage transactions that otherwise could involve the payment of a premium over prevailing market prices of our common stock. Under certain circumstances, these provisions could reduce the market price of our common stock.

As of, and after, this offering and the Concurrent Private Placement, Invus, L.P. and its affiliates own, and will own, approximately the same percentage of the outstanding shares of our common stock as owned prior to this offering and the Concurrent Private Placement. Such controlling interest in us—and the ability to maintain such controlling interest over time—may make us a less attractive target for a takeover than we otherwise might be, or render more difficult or discourage a merger proposal, tender offer or proxy contest, even if such actions were favored by our other stockholders, which could thereby deprive holders of our common stock of an opportunity to sell their shares at a premium over the prevailing market price. See “Risk Factors—Risks Related to our Common Stock—Invus, L.P. and its affiliates own a controlling interest in our outstanding common stock and may have interests which conflict with those of our other stockholders” in our Annual Report on Form 10-K for the year ended December 31, 2022 for additional information.

Future sales of our common stock, or the perception that such sales may occur, may depress our stock price.

We or our stockholders may sell shares of common stock in the future. A substantial number of shares of our common stock is reserved for issuance upon conversion of notes evidencing our current indebtedness, upon the exercise of stock options and upon vesting of restricted stock units. If we or our stockholders sell substantial amounts of our common stock (including shares issued upon the conversion of notes, exercise of stock options or vesting of restricted stock units) in the public market, or if the market perceives that such sales may occur, the market price of our common stock could fall and it may become more difficult for us to sell equity or equity-related securities in the future at a time and price that we deem appropriate. For example, following an acquisition, a significant number of shares of our common stock held by new stockholders may become freely tradable or holders of registration rights could cause us to register their shares for resale. Sales of these shares of common stock held by existing stockholders could cause the market price of our common stock to decline. We cannot predict the size of future issuances or sales of our common stock or the effect, if any, that future issuances and sales of shares of our common stock will have on the market price of our common stock.

You may experience future dilution as a result of future equity offerings.

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the

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price per share in this offering and the Concurrent Private Placement. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by any investors in this offering and the Concurrent Private Placement, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by any investors in this offering and Concurrent Private Placement.

We do not currently intend to pay dividends on our common stock, and any return to investors is expected to come, if at all, only from potential increases in the price of our common stock.

We have never declared or paid cash dividends on our capital stock, and you should not rely on an investment in our common stock to provide dividend income. We anticipate that we will retain all of our future earnings, if any, to finance the growth and development of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. In addition, our term loan agreement contains certain covenants that limit our ability to pay or make any dividend and the terms of any future debt agreements may further preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein contain certain information regarding our financial projections, plans and strategies that are forward-looking statements. We have attempted to identify forward-looking statements by terminology including “anticipate,” “believe,” “can,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “should” or “will” or the negative of these terms or other comparable terminology. These statements, which are only predictions and involve known and unknown risks, uncertainties and other important factors may include, among other things, statements which address our strategy and operating performance, events or developments that we expect or anticipate will occur in the future, such as projections of our future results of operations or of our financial condition, the regulatory status and therapeutic and commercial potential of our drug programs, the status of any collaborative agreements or clinical trials, the expected timing of the completion of our ongoing and future clinical trials and the results of such trials, including top-line data, our ability to successfully commercialize INPEFA in heart failure on the timeline and/or at the prices currently contemplated or at all, expected timing of commercialization of our other product candidates, initiation of our planned clinical trials, expected enrollment in our ongoing and future clinical trials, our research and development efforts and anticipated trends in our business.

We have based these forward-looking statements on our current expectations and projections about future events. However, there may be events in the future that we are not able to predict accurately or which we do not fully control that could cause actual results to differ materially from those expressed or implied in our forward-looking statements. Many important factors could cause actual results to differ materially from those expressed or implied by these forward-looking statements, including those discussed under “Risk Factors” beginning on page S-5 of this prospectus supplement and similar sections in the accompanying prospectus and documents incorporated by reference herein. As a result, you should not rely on such statements in making your investment decision. Except as required by applicable law, we undertake no obligation to publicly release any revisions to the forward-looking statements or reflect events or circumstances after the date of this prospectus supplement.

USE OF PROCEEDS

We estimate that the net proceeds from this offering and the Concurrent Private Placement will be approximately \$ million (or \$ million if the underwriters' option to purchase additional shares of our common stock is exercised in full and the Private Placement Purchaser exercises its proportionate preemptive right in full) after deducting underwriting discounts and commissions and estimated offering expenses.

We currently intend to use a portion of the net proceeds from this offering and the Concurrent Private Placement, together with our existing cash and cash equivalents and short-term investments, to (i) fund the commercial launch of INPEFA, and (ii) fund the continued research and development of our drug candidates and for working capital and other general corporate purposes.

The amounts that we actually expend for the commercial launch of INPEFA, research and development, acquisitions, investments or general corporate purposes will vary significantly depending on a number of factors, including our future INPEFA sales and other revenues, the amount of cash we generate from operations and the progress of our research, development and commercialization efforts. Accordingly, our management will retain broad discretion in the allocation of the net proceeds from this offering and the Concurrent Private Placement.

Pending the uses described above, we plan to invest the net proceeds from this offering and the Concurrent Private Placement in short-term or long-term, investment-grade, interest-bearing securities.

DIVIDEND POLICY

We have never paid cash dividends on our common stock. We anticipate that we will retain all of our future earnings, if any, for use in the expansion and operation of our business and do not anticipate paying cash dividends in the foreseeable future. In addition, our loan and security agreement with Oxford Finance LLC contains covenants restricting our payment of dividends. See “Risk Factors—Risks Related to this Offering—We do not currently intend to pay dividends on our common stock, and any return to investors is expected to come, if at all, only from potential increases in the price of our common stock.”

DILUTION

If you invest in our common stock, your interest will be diluted immediately to the extent of the difference between the public offering price per share you will pay in this offering and the as adjusted net tangible book value per share after this offering.

As of March 31, 2023, our net tangible book value was approximately \$43.5 million, or approximately \$0.23 per share. Net tangible book value per share represents the amount of our total tangible assets, excluding goodwill and other intangible assets, less total liabilities divided by the 189,561,819 shares of our common stock outstanding as of May 2, 2023. After giving effect to our sale of the shares of common stock in this offering and Concurrent Private Placement, after deducting underwriting discounts and commissions and estimated offering expenses at an assumed offering price of \$, the net tangible book value as of March 31, 2023 would have been approximately \$ million, or approximately \$ per share. This represents an immediate increase in net tangible book value of \$ per share to existing stockholders and an immediate dilution in net tangible book value of \$ per share to new investors purchasing shares of common stock at the public offering price.

The following table illustrates this dilution on a per share basis:

Assumed public offering price per share	\$
Net tangible book value per share as of March 31, 2023	<u>\$0.23</u>
Increase in net tangible book value per share attributable to new investors	
As adjusted net tangible book value per share after giving effect to this offering and the Concurrent Private Placement	<u>\$</u>
Dilution in net tangible book value per share to new investors	\$

If the underwriters exercise their option to purchase an additional shares of our common stock in full and the Private Placement Purchaser exercises its option to purchase an additional shares of our common stock in full, at the public offering price of \$ per share, the as adjusted net tangible book value per share after giving effect to this offering and the Concurrent Private Placement would be \$ per share, representing an immediate increase in net tangible book value to existing shareholders of \$ per share and immediate dilution in net tangible book value to new investors of \$ per share.

The foregoing table and calculations (other than the historical net tangible book value calculation) are based on 189,561,819 shares outstanding as of May 2, 2023, and excludes the following:

- 17,127,000 shares of common stock issuable upon the exercise of outstanding stock options as of March 31, 2023, with a weighted-average exercise price of \$4.25 per share;
- 5,490,000 shares of common stock issuable upon the vesting of outstanding restricted stock units as of March 31, 2023;
- 420,673 shares of common stock issuable pursuant to outstanding warrants as of March 31, 2023, with a warrant price of \$2.08 per share;
- 224,128 shares of common stock issuable pursuant to outstanding warrants as of March 31, 2023, with a warrant price of \$1.95 per share; and
- 25,224,727 shares of common stock reserved for future issuance under our 2017 Equity Incentive Plan and 2017 Non-Employee Directors' Equity Incentive Plan, as of March 31, 2023 and after giving effect to the approval by our shareholders of certain additional authorized shares of common stock thereunder on April 27, 2023.

CONCURRENT PRIVATE PLACEMENT

The Private Placement Purchaser, an affiliate of Invus, L.P., our largest stockholder, is purchasing shares of our common stock in the Concurrent Private Placement, which is exempt from the registration requirements of the Securities Act, at the same price as the price to the public in this offering for aggregate gross proceeds of \$ million. The underwriters will not receive any underwriting discounts or commissions on any shares of our common stock sold to the Private Placement Purchaser or its affiliates. The Concurrent Private Placement is contingent on the closing of this offering and the satisfaction of certain other customary conditions. In connection with the Concurrent Private Placement, we will enter into a securities purchase agreement with the Private Placement Purchaser and certain other affiliates of Invus, L.P.

UNDERWRITING

Citigroup Global Markets Inc., Jefferies LLC and Piper Sandler & Co. are acting as joint book-running managers of this offering and as representatives of the underwriters named below. Subject to the terms and conditions stated in the underwriting agreement dated the date of this prospectus, each underwriter named below has severally agreed to purchase, and we have agreed to sell to that underwriter, the number of shares of common stock set forth opposite the underwriter's name in the following table.

<u>Underwriters</u>	<u>Number of Shares</u>
Citigroup Global Markets Inc.	
Jefferies LLC	
Piper Sandler & Co.	
Total	

The underwriting agreement provides that the obligations of the underwriters to purchase the securities included in this offering are subject to approval of legal matters by counsel and to other conditions. The underwriters are obligated to purchase all the securities (other than those covered by the underwriters' option to purchase additional shares described below) if they purchase any of the securities.

Securities sold by the underwriters to the public will initially be offered at the initial public offering price set forth on the cover of this prospectus. Any securities sold by the underwriters to securities dealers may be sold at a discount from the initial public offering price not to exceed \$ _____ per share. If all the securities are not sold at the initial offering price, the underwriters may change the offering price and the other selling terms.

If the underwriters sell more securities than the total number set forth in the table above, we have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to _____ additional shares at the public offering price less the underwriting discounts and commissions. To the extent the option is exercised, each underwriter must purchase a number of additional shares approximately proportionate to that underwriter's initial purchase commitment. Any shares issued or sold under the option will be issued and sold on the same terms and conditions as the other shares that are the subject of this offering. If, and to the extent, the underwriters exercise their option to purchase additional shares, the Private Placement Purchaser will have the option to purchase a proportionate amount of additional shares pursuant to its preemptive right in an additional closing of the Concurrent Private Placement.

Our executive officers, directors and certain of our stockholders, including certain affiliates of the Private Placement Purchaser (each, a "Lock-Up Party"), have agreed (subject, in the case of the Private Placement Purchaser, to certain qualifications and exceptions) not to, for a period of 60 days from the date of this prospectus supplement (such period, the "Lock-Up Period"), without the prior written consent of Citigroup Global Markets Inc., Jefferies LLC and Piper Sandler & Co., in their sole discretion, (1) offer, pledge, hedge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of our common stock beneficially owned (as such term is used in Rule 13d-3 under the Securities Exchange Act of 1934, as amended (the "Exchange Act")), by such Lock-Up Party or any other securities so owned convertible into or exercisable or exchangeable for our common stock or (2) enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of our common stock, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of our common stock or such other securities, in cash or otherwise. The restrictions described in the foregoing sentence shall not apply to (a) transactions relating to shares of our common stock or other securities acquired in open market transactions after the completion of this offering, provided that no filing under Section 16(a) of the Exchange Act shall be required or shall be voluntarily made in connection with subsequent sales of our common stock or other securities acquired in such open market transactions, (b) any surrender of shares of our common stock (or options to purchase shares of our common stock) to us by such Lock-Up Party in satisfaction of (i) any federal, state or local taxes required by

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law to be withheld with respect to the vesting of shares of our common stock or the exercise of stock options to purchase our common stock and/or (ii) the exercise price payable to us with respect to the exercise of stock options to purchase our common stock, in each case granted under a stock incentive plan or stock purchase plan of ours described in this prospectus supplement and the accompanying prospectus and the documents incorporated by reference herein and in accordance with the terms of any such instrument as in effect on or before the date hereof, (c) transfers of shares of our common stock or any security convertible into our common stock as a bona fide gift, (d) distributions of shares of our common stock or any security convertible into our common stock to limited partners, members, stockholders or equityholders of such Lock-Up Party, (e) transfers to such Lock-Up Party's affiliates or to any investment fund or other entity controlled or managed by such Lock-Up Party, (f) transfers to immediate family of such Lock-Up Party, to a trust all of the beneficiaries of which are such Lock-Up Party and/or members of his or her immediate family or to a corporation, partnership, limited partnership or limited liability company all of the stockholders, partners and members of which are such Lock-Up Party and/or members of his or her immediate family, in each case for estate planning purposes, (g) transfers by will or other testamentary document, or intestacy; *provided* that (i) in the case of any transfer or distribution pursuant to clauses (c) – (g) each donee, distributee or transferee shall sign and deliver a lock-up agreement substantially in the form of the lock-up agreement described herein, (ii) in the case of any surrender, transfer or distribution pursuant to clauses (b) and (g), no filing under Section 16(a) of the Exchange Act, reporting a reduction in beneficial ownership of shares of our common stock, shall be voluntarily made during the Lock-Up Period and if any filing under Section 16(a) of the Exchange Act shall be legally required during the Lock-Up Period, such filing, report or announcement shall clearly indicate in the footnotes thereto the nature and conditions of such transfer and (iii) in the case of any surrender, transfer or distribution pursuant to clauses (c) – (f), no filing under Section 16(a) of the Exchange Act, reporting a reduction in beneficial ownership of shares of our common stock, shall be required or shall be voluntarily made during the Lock-Up Period, (h) the sale of securities in a registered public offering pursuant to such Lock-Up Party's incidental, or "piggy-back," registration rights in connection with registration statements proposed to be filed by us for any public offering of securities of ours after this public offering, (i) any transfers, surrenders or distributions, or offers to take any such action, in connection with a bona fide third party takeover bid made to all or substantially all holders of our common stock or any other acquisition, merger, consolidation, stock exchange or other similar transaction whereby all or substantially all of our common stock is acquired by a third party; *provided* that in the event the third party takeover bid or other acquisition, merger, consolidation, stock exchange or other similar transaction is not completed, such Lock-Up Party shall remain subject to the restrictions described herein, (j) the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of our common stock; *provided* that such plan does not provide for the transfer of our common stock during the Lock-Up Period, except as otherwise permitted herein, and no public announcement or filing under the Exchange Act regarding the establishment of such plan shall be required of or voluntarily made by or on behalf of such Lock-Up Party or us during the Lock-Up Period or (k) by operation of law, such as pursuant to a qualified domestic order, divorce settlement, divorce decree or separation agreement; *provided* that if any filing under Section 16(a) of the Exchange Act shall be legally required during the Lock-Up Period, such filing, report or announcement shall clearly indicate in the footnotes thereto the nature and conditions of such transfer.

We have agreed not to, without the prior written consent of Citigroup Global Markets Inc., Jefferies LLC and Piper Sandler & Co., in their sole discretion, offer, sell, contract to sell, pledge, hedge, or otherwise dispose of, (or enter into any transaction which is designed to, or might reasonably be expected to, result in the disposition (whether by actual disposition or effective economic disposition due to cash settlement or otherwise) by us or any of our affiliates or any person in privity with us or any of our affiliates) directly or indirectly, including the submission or filing (or participation in the submission or filing) of a registration statement with the SEC in respect of, or establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Exchange Act, any other shares of our common stock or any securities convertible into, or exercisable, or exchangeable for, shares of our common stock; or publicly announce an intention to effect any such transaction, for a period of 60 days from the date of this prospectus supplement (such period, the "Company Lock-Up Period"), *provided, however*, that we may: (i) effect the

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transactions contemplated hereby and issue shares of our common stock pursuant to the Concurrent Private Placement; (ii) issue warrants to purchase shares of our common stock with a value equal to up to \$656,250, pursuant to an election to obtain a Term C Loan within 60 days upon the FDA's approval of INPEFA pursuant to our Loan and Security Agreement, dated March 17, 2022, as amended, with Oxford Finance, LLC, provided that if any filing under Section 16(a) of the Exchange Act shall be legally required during the Company Lock-Up Period, such filing, report or announcement shall clearly indicate in the footnotes thereto the nature and conditions of such transfer; (iii) grant options, restricted stock units or other equity awards or issue shares of our common stock to our employees, officers, directors, advisors or consultants pursuant to our employee benefit plans, *provided*, that each recipient of such securities that is a newly appointed director or executive officer agree to restrictions on the resale of securities that are consistent with the provisions set forth in the lock-up agreement described above; (iv) file one or more registration statements on Form S-8 relating to stock options or our employee benefit plans, and *provided, further*, that each recipient of such securities that is a newly appointed director or executive officer agrees to restrictions on the resale of securities that are consistent with the provisions set forth in the lock-up agreement described above and (v) enter into any acquisition, merger, consolidation, stock exchange or similar transaction whereby all or substantially all of our common stock is acquired by a third party, which is approved by our board of directors; *provided* that (A) any such transaction is not solicited by us and (B) in the event the acquisition, merger, consolidated, stock exchange or other similar transaction is not completed, we will remain subject to the restrictions described herein.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "LXXR." We have applied to have the shares of common stock that we are issuing and selling in this offering listed on Nasdaq. Listing will be subject to us fulfilling all the listing requirements of Nasdaq.

The following table shows the underwriting discounts and commissions that we will pay to the underwriters in connection with this offering. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

Per Share	Paid by Lexicon Pharmaceuticals, Inc.	
	No Exercise	Full Exercise
Total	\$	\$

We estimate that our total expenses of this offering and the Concurrent Private Placement will be approximately \$. We have agreed to reimburse the underwriters for certain legal fees and expenses, including expenses related to the clearing of this offering with the Financial Industry Regulatory Authority, Inc. ("FINRA"), in an amount not to exceed \$20,000 in the aggregate.

In connection with the offering, the underwriters may purchase and sell shares in the open market. Purchases and sales in the open market may include short sales, purchases to cover short positions, which may include purchases pursuant to the underwriters' option to purchase additional shares, and stabilizing purchases.

- Short sales involve secondary market sales by the underwriters of a greater number of shares than they are required to purchase in the offering.
 - "Covered" short sales are sales of shares in an amount up to the number of shares represented by the underwriters' option to purchase additional shares.
 - "Naked" short sales are sales of shares in an amount in excess of the number of shares represented by the underwriters' option to purchase additional shares.
- Covering transactions involve purchases of shares either pursuant to the underwriters' option to purchase additional shares or in the open market in order to cover short positions.
 - To close a naked short position, the underwriters must purchase shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may

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be downward pressure on the price of the shares in the open market after pricing that could adversely affect investors who purchase in the offering.

- To close a covered short position, the underwriters must purchase shares in the open market or must exercise the option to purchase additional shares. In determining the source of shares to close the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the underwriters' option to purchase additional shares.
- Stabilizing transactions involve bids to purchase shares so long as the stabilizing bids do not exceed a specified maximum.

Purchases to cover short positions and stabilizing purchases, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the shares. They may also cause the price of the shares to be higher than the price that would otherwise exist in the open market in the absence of these transactions. The underwriters may conduct these transactions on The Nasdaq Global Select Market, in the over-the-counter market or otherwise. If the underwriters commence any of these transactions, they may discontinue them at any time.

Relationships

The underwriters are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have in the past performed commercial banking, investment banking and advisory services for us from time to time for which they have received customary fees and reimbursement of expenses and may, from time to time, engage in transactions with and perform services for us in the ordinary course of their business for which they may receive customary fees and reimbursement of expenses. In the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (which may include bank loans and/or credit default swaps) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make because of any of those liabilities.

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area (each a "Relevant Member State"), no securities have been offered or will be offered pursuant to the offering to the public in that Relevant Member State prior to the publication of a prospectus in relation to the securities which has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the competent authority in that Relevant Member State, all in accordance with the Prospectus Regulation, except that the securities may be offered to the public in that Relevant Member State at any time:

- (a) to any legal entity which is a qualified investor as defined under Article 2 of the Prospectus Regulation;
- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or

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- (c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of the securities shall require us or any of the underwriters or any of their respective affiliates to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

For the purposes of this provision, the expression an “offer to the public” in relation to the securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any securities to be offered so as to enable an investor to decide to purchase any securities, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129.

Each person in a Relevant Member State who receives any communication in respect of, or who acquires any securities under, the offering contemplated hereby will be deemed to have represented warranted and agreed to and with each of the underwriters and their respective affiliates and us that:

- (a) it is a qualified investor within the meaning of the Prospectus Regulation; and
- (b) in the case of any securities acquired by it as a financial intermediary, as that term is used in Article 5 of the Prospectus Regulation, (i) the securities acquired by it in the offering have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in any Relevant Member State other than qualified investors, as that term is defined in the Prospectus Regulation, or have been acquired in other circumstances falling within the points (a) to (d) of Article 1(4) of the Prospectus Regulation and the prior consent of the representatives has been given to the offer or resale; or (ii) where the securities have been acquired by it on behalf of persons in any Relevant Member State other than qualified investors, the offer of those securities to it is not treated under the Prospectus Regulation as having been made to such persons.

We, the underwriters and their respective affiliates, and others will rely upon the truth and accuracy of the foregoing representation, acknowledgement and agreement. Notwithstanding the above, a person who is not a qualified investor and who has notified the representatives of such fact in writing may, with the prior consent of the representatives, be permitted to acquire securities in the offering.

Notice to Prospective Investors in the United Kingdom

This prospectus supplement and any other material in relation to the securities described herein is only being distributed to, and is only directed at, and any investment or investment activity to which this prospectus supplement relates is available only to, and will be engaged in only with persons who are (i) persons having professional experience in matters relating to investments who fall within the definition of investment professionals in Article 19(5) of the FPO; or (ii) high net worth entities falling within Article 49(2)(a) to (d) of the FPO; (iii) outside the United Kingdom; or (iv) persons to whom an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the FSMA) in connection with the issue or sale of any securities may otherwise lawfully be communicated or caused to be communicated, all such persons together being referred to as Relevant Persons. The securities are only available in the United Kingdom to, and any invitation, offer or agreement to purchase or otherwise acquire the securities will be engaged in only with, the Relevant Persons. This prospectus supplement and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other person in the United Kingdom. Any person in the United Kingdom that is not a Relevant Person should not act or rely on this prospectus supplement or any of its contents.

No securities have been offered or will be offered pursuant to the offering to the public in the United Kingdom prior to the publication of a prospectus in relation to the securities which has been approved by the Financial Conduct Authority, except that the securities may be offered to the public in the United Kingdom at any time:

- (a) to any legal entity which is a qualified investor as defined under Article 2 of the UK Prospectus Regulation;

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- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the UK Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or
- (c) in any other circumstances falling within Section 86 of the FSMA,

provided that no such offer of the securities shall require us or any underwriter or any of their respective affiliates to publish a prospectus pursuant to Section 85 of the FSMA or supplement a prospectus pursuant to Article 23 of the UK Prospectus Regulation.

For the purposes of this provision, the expression an “offer to the public” in relation to the securities in the United Kingdom means the communication in any form and by any means of sufficient information on the terms of the offer and any securities to be offered so as to enable an investor to decide to purchase or subscribe for any securities and the expression “UK Prospectus Regulation” means Regulation (EU) 2017/1129 as it forms part of domestic law by virtue of the European Union (Withdrawal) Act 2018.

Each person in the United Kingdom who acquires any securities in the offering or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with us, the underwriters and their respective affiliates that it meets the criteria outlined in this section.

Notice to Prospective Investors in Canada

The securities may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser’s province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser’s province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in France

Neither this prospectus supplement nor any other offering material relating to the securities described in this prospectus supplement has been submitted to the clearance procedures of the Autorité des Marchés Financiers or of the competent authority of another member state of the European Economic Area and notified to the Autorité des Marchés Financiers. The securities have not been offered or sold and will not be offered or sold, directly or indirectly, to the public in France. Neither this prospectus supplement nor any other offering material relating to the securities has been or will be:

- released, issued, distributed or caused to be released, issued or distributed to the public in France; or
- used in connection with any offer for subscription or sale of the securities to the public in France.

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Such offers, sales and distributions will be made in France only:

- to qualified investors (*investisseurs qualifiés*) and/or to a restricted circle of investors (*cercle restreint d'investisseurs*), in each case investing for their own account, all as defined in, and in accordance with articles L.411-2, D.411-1, D.411-2, D.734-1, D.744-1, D.754-1 and D.764-1 of the French Code monétaire et financier;
- to investment services providers authorized to engage in portfolio management on behalf of third parties; or
- in a transaction that, in accordance with article L.411-2-II-1° -or-2° -or 3° of the French Code monétaire et financier and article 211-2 of the General Regulations (*Règlement Général*) of the Autorité des Marchés Financiers, does not constitute a public offer (*appel public à l'épargne*).

The securities may be resold directly or indirectly, only in compliance with articles L.411-1, L.411-2, L.412-1 and L.621-8 through L.621-8-3 of the French Code monétaire et financier.

Notice to Prospective Investors in Hong Kong

The securities may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong), or (ii) to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a “prospectus” within the meaning of the Companies Ordinance (Cap. 32, Laws of Hong Kong) and no advertisement, invitation or document relating to the securities may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to securities which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Notice to Prospective Investors in Japan

The securities offered in this prospectus supplement have not been and will not be registered under the Financial Instruments and Exchange Law of Japan. The securities have not been offered or sold and will not be offered or sold, directly or indirectly, in Japan or to or for the account of any resident of Japan (including any corporation or other entity organized under the laws of Japan), except (i) pursuant to an exemption from the registration requirements of the Financial Instruments and Exchange Law and (ii) in compliance with any other applicable requirements of Japanese law.

Notice to Prospective Investors in Singapore

This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the securities may not be circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (the “SFA”), (ii) to a relevant person pursuant to Section 275(1), or any person pursuant to Section 275(1A), and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to compliance with conditions set forth in the SFA.

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Where the securities are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

shares, debentures and units of shares and debentures of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the securities pursuant to an offer made under Section 275 of the SFA except:

- to an institutional investor (for corporations, under Section 274 of the SFA) or to a relevant person defined in Section 275(2) of the SFA, or to any person pursuant to an offer that is made on terms that such shares, debentures and units of shares and debentures of that corporation or such rights and interest in that trust are acquired at a consideration of not less than S\$200,000 (or its equivalent in a foreign currency) for each transaction, whether such amount is to be paid for in cash or by exchange of securities or other assets, and further for corporations, in accordance with the conditions specified in Section 275 of the SFA;
- where no consideration is or will be given for the transfer; or
- where the transfer is by operation of law.

Solely for the purposes of its obligations pursuant to section 309B(1)(a) and 309B(1)(c) of the SFA and the Securities and Futures (Capital Markets Products) Regulations 2018 of Singapore (the "CMP Regulations 2018"), we have determined, and hereby notify all relevant persons (as defined in Section 309A(1) of the SFA), that the securities are "prescribed capital markets products" (as defined in the CMP Regulations 2018) and Excluded Investment Products (as defined in MAS Notice SFA 04-N12: Notice on the Sale of Investment Products; and MAS notice FAA-N16: Notice on Recommendations on Investment Products).

Notice to Prospective Investors in Switzerland

We have not and will not register with the Swiss Financial Market Supervisory Authority (FINMA) as a foreign collective investment scheme pursuant to Article 119 of the Federal Act on Collective Investment Scheme of 23 June 2006, as amended (CISA), and accordingly the securities being offered pursuant to this prospectus supplement have not and will not be approved, and may not be licenseable, with FINMA. Therefore, the securities have not been authorized for distribution by FINMA as a foreign collective investment scheme pursuant to Article 119 CISA and the securities offered hereby may not be offered to the public (as this term is defined in Article 3 CISA) in or from Switzerland. The securities may solely be offered to "qualified investors," as this term is defined in Article 10 CISA, and in the circumstances set out in Article 3 of the Ordinance on Collective Investment Scheme of 22 November 2006, as amended (CISO), such that there is no public offer. Investors, however, do not benefit from protection under CISA or CISO or supervision by FINMA. This prospectus supplement and any other materials relating to the securities are strictly personal and confidential to each offeree and do not constitute an offer to any other person. This prospectus supplement may only be used by those qualified investors to whom it has been handed out in connection with the offer described in this prospectus supplement and may neither directly or indirectly be distributed or made available to any person or entity other than its recipients. It may not be used in connection with any other offer and shall in particular not be copied and/or distributed to the public in Switzerland or from Switzerland. This prospectus supplement does not constitute an issue prospectus as that term is understood pursuant to Article 652a and/or 1156 of the Swiss Federal Code of Obligations. We have not applied for a listing of the securities on the SIX Swiss Exchange or any other regulated securities market in Switzerland, and consequently, the information presented in this prospectus supplement does not necessarily comply with the information standards set out in the listing rules of the SIX Swiss Exchange and corresponding prospectus schemes annexed to the listing rules of the SIX Swiss Exchange.

LEGAL MATTERS

The validity of the shares of common stock being offered by this prospectus will be passed upon for us by Vinson & Elkins L.L.P., Houston, Texas. The underwriters are being represented in connection with this offering by Cooley LLP, San Francisco, California.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022, and the effectiveness of our internal control over financial reporting as of December 31, 2022, as set forth in their reports, which are incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” the information we have filed with it, which means that we can disclose important information to you by referring you to those documents. The information we incorporate by reference is an important part of this prospectus supplement, and later information that we file with the SEC will automatically update and supersede this information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus supplement and accompanying prospectus to the extent that a statement contained in this prospectus supplement or the accompanying prospectus modifies or replaces that statement.

We incorporate by reference the documents listed below (excluding, in each case, any information therein deemed “furnished” rather than “filed”) that we have previously filed with the SEC and any future documents (excluding, in each case, any information therein deemed “furnished” rather than “filed”) filed with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act subsequent to the date of this prospectus supplement and prior to the termination of the offering of the securities covered by this prospectus supplement:

- our Annual Report on Form 10-K for the year ended December 31, 2022 filed on [March 3, 2023](#), including information specifically incorporated by reference into such Annual Report on Form 10-K from our Proxy Statement for our 2023 Annual Meeting of Stockholders filed on [March 17, 2023](#);
- our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2023 filed on [May 4, 2023](#);
- our Current Reports on Forms 8-K and 8-K/A filed on [January 4, 2023](#), [April 27, 2023](#), [May 2, 2023](#) and [May 8, 2023](#); and
- the description of our common stock contained in our registration statement on [Form 8-A](#) filed with the SEC on March 27, 2000, including any amendment to that Form that we may file in the future for the purpose of updating the description of our capital stock.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus supplement will be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or in any other subsequently filed document which also is or is deemed to be incorporated by reference in this prospectus supplement modifies or supersedes that statement. Any statement that is modified or superseded will not constitute a part of this prospectus supplement, except as so modified or superseded.

You should only rely on the information contained in this prospectus supplement or in documents incorporated or deemed to be incorporated in this prospectus supplement, unless that statement has been subsequently modified or superseded as described above prior to the time you make your investment decision.

Upon your written or oral request, we will provide you, at no cost, a copy of any or all of the documents incorporated by reference in this prospectus supplement, other than the exhibits to those documents, unless the exhibits are specifically incorporated by reference into this prospectus supplement. You may request a copy of these documents by contacting:

Lexicon Pharmaceuticals, Inc.
Attention: General Counsel
2445 Technology Forest Blvd., 11th Floor
The Woodlands, Texas 77381
Phone: (281) 863-3000

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information regarding registrants, like us, that file electronically with the SEC. The address of the SEC's Internet site is www.sec.gov.

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and other filings with the SEC are available, free of charge, through our website, as soon as reasonably practicable after those reports or filings are electronically filed with or furnished to the SEC. Information on our website or any other website is not incorporated by reference into this prospectus supplement and does not constitute a part of this prospectus supplement.

This prospectus supplement is part of a registration statement we filed with the SEC relating to the securities we may offer. As permitted by SEC rules, this prospectus supplement does not contain all of the information we have included in the registration statement and the accompanying exhibits and schedules we have filed with the SEC. You should refer to the registration statement, exhibits and schedules for more information about us and the securities. The registration statements, exhibits and schedules are available at the SEC or through its website.

\$200,000,000



Lexicon Pharmaceuticals, Inc.

Common Stock
Preferred Stock
Debt Securities
Warrants
Rights
Units

We may offer common stock, preferred stock, debt securities, warrants and/or rights, either individually or in units, from time to time in one or more offerings in amounts, at prices and on terms to be determined in light of market conditions at the time of sale. We may also offer common stock or preferred stock upon conversion of debt securities, common stock upon conversion of preferred stock or common stock, preferred stock or debt securities upon the exercise of warrants or rights.

Each time we sell these securities, we will provide a supplement to this prospectus that contains specific information about the offering. The supplement may also add, update or change information contained in this prospectus. You should carefully read this prospectus and any supplement before you invest.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "LXRX". The prospectus supplement will contain information, where applicable, regarding any other listing on The Nasdaq Global Select Market or any securities exchange of the securities covered by the prospectus supplement. The last reported sale price of our common stock on August 4, 2021 was \$3.41 per share.

Investing in our securities involves risks. See "[Risk Factors](#)" on page 4.

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

The date of this prospectus is September 14, 2021.

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ABOUT THIS PROSPECTUS

This prospectus is part of a “shelf” registration statement that we filed with the Securities and Exchange Commission, or the SEC. Under this shelf registration process, we may sell, from time to time, an indeterminate amount of any combination of the securities described in this prospectus in one or more offerings. This prospectus provides you with a general description of the securities we may offer, which is not meant to be a complete description of each security. Each time that we sell securities, a prospectus supplement containing specific information about the terms of that offering will be provided, including the specific amounts, prices and terms of the securities offered and the manner in which they will be offered. The prospectus supplement and any other offering material may also add to, update or change information contained in this prospectus or in documents we have incorporated by reference into this prospectus. We urge you to read both this prospectus and any prospectus supplement and any other offering material (including any free writing prospectus) prepared by or on behalf of us for a specific offering of securities, together with the additional information described under the heading “Where You Can Find More Information” on page 28 of this prospectus.

In this prospectus, “Lexicon,” “Lexicon Pharmaceuticals,” “we,” “us” and “our” refer to Lexicon Pharmaceuticals, Inc. and its subsidiaries. We own or have rights to trademarks or trade names that we use in connection with the operation of our business. The Lexicon name and logo are registered trademarks of Lexicon Pharmaceuticals, Inc.

You should rely only on the information contained in this prospectus, any prospectus supplement or any free writing prospectus prepared by or on behalf of us and any documents incorporated into this prospectus by reference. We have not authorized anyone to provide you with information different from that contained in this prospectus or the documents incorporated by reference herein. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are not making an offer to sell or soliciting an offer to purchase these securities in any jurisdiction where the offer or sale is not permitted. This prospectus may only be used where it is legal to sell these securities. The information contained in this prospectus, the documents incorporated by reference herein and any supplements to this prospectus are accurate only as of the dates of their respective covers or earlier dates as specified therein, regardless of the time of delivery of this prospectus or any supplement to this prospectus or of any sale of these securities.

LEXICON PHARMACEUTICALS, INC.

We are a biopharmaceutical company with a mission of pioneering medicines that transform patients' lives. We are devoting most of our resources to the research and development of our most advanced drug candidates:

- We are developing LX9211, an orally-delivered small molecule drug candidate, as a treatment for neuropathic pain. We have reported results from two Phase 1 clinical trials of LX9211 and are now conducting a Phase 2 clinical trial of LX9211 in diabetic peripheral neuropathic pain and a second Phase 2 clinical trial of LX9211 in post-herpetic neuralgia. LX9211 has received Fast Track designation from the FDA for development in diabetic peripheral neuropathic pain.
- We are developing sotagliflozin, an orally-delivered small molecule drug candidate, as a treatment for heart failure and type 1 diabetes. We have reported positive results from two Phase 3 clinical trials evaluating the effect of sotagliflozin on long-term outcomes related to cardiovascular death and heart failure in approximately 10,500 and 1,200 patients, respectively. We are now preparing an application for regulatory approval to market sotagliflozin for heart failure in the United States and, if approved, for the commercial launch of sotagliflozin in the United States.

We have reported positive results from three Phase 3 clinical trials evaluating the effect of sotagliflozin on type 1 diabetes in approximately 800, 800 and 1,400 patients, respectively. The FDA issued a complete response letter regarding our application for regulatory approval to market sotagliflozin for type 1 diabetes in the United States and, at our request, has issued a public Notice of Opportunity for Hearing on whether there are grounds for denying approval of our application. Sotagliflozin has been approved in the European Union for use as an adjunct to insulin therapy in the treatment of type 1 diabetes, but has not yet been commercially launched.

- We are conducting preclinical research and development and preparing to conduct clinical development of compounds from a number of additional drug programs originating from our internal drug discovery efforts.

LX9211 originated from our collaborative neuroscience drug discovery efforts with Bristol-Myers Squibb, and sotagliflozin and compounds from a number of additional drug programs originated from our own internal drug discovery efforts. Those efforts were driven by a systematic, target biology-driven approach in which we used gene knockout technologies and an integrated platform of advanced medical technologies to systematically study the physiological and behavioral functions of almost 5,000 genes in mice and assessed the utility of the proteins encoded by the corresponding human genes as potential drug targets. We have identified and validated in living animals, or in vivo, more than 100 targets with promising profiles for drug discovery.

We are working both independently and through collaborations and strategic alliances with third parties to capitalize on our drug target discoveries and drug discovery and development programs. We seek to retain exclusive or co-exclusive rights to the benefits of certain drug discovery and development programs by developing and commercializing drug candidates from those programs internally, particularly in the United States for indications treated by specialist physicians. We seek to collaborate with other pharmaceutical and biotechnology companies with respect to drug discovery or the development and commercialization of certain of our drug candidates, particularly with respect to commercialization in territories outside the United States or commercialization in the United States for indications treated by primary care physicians, or when the collaboration may otherwise provide us with access to expertise and resources that we do not possess internally or are complementary to our own. Our collaborations and strategic alliances include arrangements with TerSera Therapeutics LLC, under which we are eligible to receive milestone and royalty payments relating to telotristat ethyl in biliary tract cancer, and with Genentech, Inc., under which we are eligible to receive milestone and royalty payments relating to its UTTR1147a (IL-22 Fc) biotherapeutic drug candidate.

Lexicon Pharmaceuticals was incorporated in Delaware in July 1995 and commenced operations in September 1995. Our corporate headquarters are located at 2445 Technology Forest Blvd., 11th Floor, The

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Woodlands, Texas 77381, and our telephone number is (281) 863-3000. Our common stock is listed on The Nasdaq Global Select Market under the symbol "LXRX."

Our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are made available free of charge on our corporate website located at www.lexpharma.com as soon as reasonably practicable after the filing of those reports with the Securities and Exchange Commission. Information found on or through our website is not incorporated herein by reference and should not be considered part of this prospectus or any prospectus supplement.

RISK FACTORS

An investment in our securities involves a significant degree of risk. Before you invest in our securities, you should carefully consider those risk factors described under, but not limited to, the heading “Risk Factors” in our most recent annual report on Form 10-K, any subsequently filed quarterly reports on Form 10-Q and any subsequently filed current reports on Form 8-K (excluding any information furnished pursuant to Item 2.02 or Item 7.01 on any current report on Form 8-K), which are incorporated herein by reference, and those risk factors that may be included in any applicable prospectus supplement, together with all of the other information included in this prospectus, any prospectus supplement and the documents we incorporate by reference, in evaluating an investment in our securities. If any of these risks were actually to occur, our business, financial condition or results of operations could be materially adversely affected. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations and financial condition.

For more information about our SEC filings, please see “Where You Can Find More Information” and “Documents Incorporated By Reference” on page 28 of this prospectus. See also “Special Note Regarding Forward-Looking Statements” on page 24 of this prospectus.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 230 million shares of common stock, \$0.001 par value, and five million shares of preferred stock, \$0.01 par value. As of August 4, 2021, there were 144,474,452 shares of our common stock issued and outstanding, 1,164,998 shares of our common stock issued and held in treasury and no shares of preferred stock outstanding.

The following summary description of our capital stock is based on the provisions of our second amended and restated certificate of incorporation, second amended and restated bylaws and the applicable provisions of the Delaware General Corporation Law. This information may not be complete in all respects and is qualified entirely by reference to the provisions of our second amended and restated certificate of incorporation, second amended and restated bylaws and the Delaware General Corporation Law. For information on how to obtain copies of our second amended and restated certificate of incorporation and second amended and restated bylaws, see “Where You Can Find More Information” on page 28 of this prospectus.

Common Stock

The holders of common stock are entitled to one vote for each share held of record on all matters submitted to a vote of the stockholders and do not have cumulative voting rights. Accordingly, holders of a majority of the shares of common stock entitled to vote in any election of directors may elect all of the directors standing for election. Subject to preferences that may be applicable to any outstanding shares of preferred stock, the holders of common stock are entitled to receive ratably such dividends as may be declared by the board of directors out of funds legally available therefor. Upon the liquidation, dissolution or winding up of Lexicon, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preferences of any outstanding shares of preferred stock. Holders of 20% or more of our issued and outstanding common stock have (a) customary preemptive rights related to the issuance of certain of our securities and (b) consent rights prior us taking any of the following actions: (i) creating or issuing any new class or series of shares of capital stock (or securities convertible into or exercisable for shares of capital stock) having rights, preferences or privileges senior to or on parity with the common stock, (ii) subject to certain exceptions, repurchasing, retiring, redeeming or otherwise acquiring any of our equity securities (or securities convertible into or exchangeable for equity securities) or any subsidiary and (iii) adopting, or proposing to adopt, or maintaining any shareholders’ rights plan, “poison pill” or other similar plan or agreement, unless such stockholder is exempt from such plan or agreement. There are no redemption or sinking fund provisions applicable to our common stock. All outstanding shares of our common stock are, and all shares of common stock that may be issued under this prospectus will be, fully paid and non-assessable.

Preferred Stock

Pursuant to our second amended and restated certificate of incorporation, our board of directors has the authority, without further action by the stockholders, to issue up to five million shares of preferred stock, in one or more series. Our board of directors is authorized to fix or alter from time to time the designation, powers, preferences and rights of the shares of each series of preferred stock, including dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences and sinking fund terms. Our board of directors may also establish from time to time the number of shares constituting any series of preferred stock, and to increase or decrease the number of shares of any series subsequent to the issuance of shares of that series, but not below the number of shares of any series then outstanding.

We will fix the rights, preferences, privileges and restrictions of the preferred stock of each series in the certificate of designation relating to that series. We will incorporate by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report filed under the Exchange Act, the form of any

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certificate of designation that describes the terms of the series of preferred stock we are offering before the issuance of the related series of preferred stock. This description will include:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price;
- the dividend rate, period and payment date and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the provisions for a sinking fund, if any;
- the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price, or how it will be calculated, and the conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;
- voting rights, if any, of the preferred stock;
- preemption rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;
- any limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the preferred stock.

If we issue shares of preferred stock under this prospectus, the shares will be fully paid and non-assessable and will not have, or be subject to, any preemptive or similar rights.

The Delaware General Corporation Law provides that the holders of preferred stock will have the right to vote separately as a class on any proposal involving fundamental changes in the rights of holders of that preferred stock. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

The issuance of preferred stock could adversely affect the voting power, conversion or other rights of holders of common stock. Preferred stock could be issued quickly with terms designed to delay or prevent a change in control of our company or make removal of management more difficult. Additionally, the issuance of preferred stock may have the effect of decreasing the market price of our common stock.

Arrangements with Invus

In June 2007, we entered into a securities purchase agreement with Invus, L.P., under which Invus, L.P. made an initial investment in our common stock in August 2007. Invus, L.P. and its affiliates, which we collectively refer to as Invus, have subsequently made additional investments in our common stock and currently own approximately 52.3% of our outstanding common stock.

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Board of Directors. Concurrently with the execution of the securities purchase agreement, we entered into a stockholders' agreement with Invus, L.P. under which Invus has the right to designate a number of directors equal to the percentage of all the outstanding shares of our common stock owned by Invus, rounded up to the nearest whole number of directors. Invus has designated three of the nine current members of our board of directors. While Invus has not presently exercised its director designation rights in full, it may exercise them at any time in the future in its sole discretion. To facilitate the exercise of such rights, we have agreed, upon written request from Invus, to take all necessary actions in accordance with our obligations under the stockholders' agreement to (a) increase the number of directors to the number specified by Invus (which number shall be no greater than reasonably necessary for the exercise of Invus' director designation rights under the stockholders' agreement) and (b) cause the appointment to the newly created directorships of directors so designated by Invus pursuant to its rights under the stockholders' agreement.

Invus also has the right to require proportionate representation of Invus-appointed directors on the audit, compensation and corporate governance committees of our board of directors, subject to certain restrictions. Invus-designated directors currently serve as one of the three members of each of the compensation committee and the corporate governance committee of our board of directors. No Invus-designated directors currently serve on the audit committee of our board of directors.

The provisions of the stockholders' agreement relating to Invus' rights to designate members of our board of directors and its audit, compensation and corporate governance committees will terminate if the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates falls below 10%. Invus also has the right to terminate these provisions at any time in its discretion.

Registration Rights. Concurrently with the execution of the securities purchase agreement, we also entered into a registration rights agreement with Invus, L.P., pursuant to which Invus has certain demand and piggyback registration rights with respect to shares of our common stock held by them. Invus has waived these registration rights with respect to any offerings of our securities pursuant to this prospectus.

Preemptive and Consent Rights. Our second amended and restated certificate of incorporation grants holders of 20% or more of our issued and outstanding common stock (a) customary preemptive rights related to the issuance of certain of our securities and (b) consent rights prior us taking any of the following actions: (i) creating or issuing any new class or series of shares of capital stock (or securities convertible into or exercisable for shares of capital stock) having rights, preferences or privileges senior to or on parity with the common stock, (ii) subject to certain exceptions, repurchasing, retiring, redeeming or otherwise acquiring any of our equity securities (or securities convertible into or exchangeable for equity securities) or any subsidiary and (iii) adopting, or proposing to adopt, or maintaining any shareholders' rights plan, "poison pill" or other similar plan or agreement, unless such stockholder is exempt from such plan or agreement. Based on Invus' current ownership interest in our common stock, Invus possesses such preemptive and consent rights.

Anti-Takeover Effects of Provisions of Delaware Law and Our Charter Documents

Delaware Takeover Statute. We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, the statute prohibits a publicly-held Delaware corporation such as Lexicon from engaging in a business combination with an interested stockholder for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner. For purposes of Section 203, a business combination includes a merger, asset sale or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns (or within three years prior, did own) 15% or more of our voting stock.

Charter Documents. Our second amended and restated certificate of incorporation requires that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting

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of stockholders and may not be effected by a consent in writing. Additionally, our second amended and restated certificate of incorporation:

- does not provide for the use of cumulative voting in the election of directors;
- provides for a board of directors, classified into three classes of directors;
- provides that the authorized number of directors may be changed only by resolution of our board of directors; and
- provides for the authority of our board of directors to issue up to five million shares of “blank check” preferred stock and to determine the price, powers, preferences and rights of these shares, without stockholder approval.

Our second amended and restated bylaws provide that candidates for director may be nominated only by our board of directors or by a stockholder who gives written notice to us not less than 120 days nor more than 150 days in advance of the first anniversary of the date of our proxy statement relating to the previous year’s annual meeting of stockholders. The authorized number of directors is fixed in accordance with our second amended and restated certificate of incorporation. Our board of directors currently consists of nine members, divided into three classes. As a result, a portion of the board of directors will be elected each year. The board of directors may appoint new directors to fill vacancies or newly created directorships. Our second amended and restated bylaws also limit who may call a special meeting of stockholders.

Delaware law and these charter provisions may have the effect of deterring hostile takeovers or delaying changes in control of our management, which could depress the market price of our common stock.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Inc. The transfer agent for any series of preferred stock will be named and described in the prospectus supplement for that series.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus and the related indenture. While the terms summarized below will apply generally to any debt securities we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. If we so indicate in the prospectus supplement, the terms of any debt securities offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We may offer debt securities in the form of either senior debt securities or subordinated debt securities. Unless otherwise specified in a supplement to this prospectus, the debt securities will be our direct, unsecured obligations and will rank equally with all of our other unsecured and unsubordinated indebtedness.

The debt securities will be issued under an indenture between us and a trustee. The following summary of the general features of the debt securities to be governed by the indenture is subject to, and qualified in its entirety by reference to, the provisions of the indenture applicable to a particular series of debt securities. We have filed a form of indenture as an exhibit to the registration statement which includes this prospectus. Capitalized terms used in the summary have the meanings specified in the indenture.

General

The terms of each series of debt securities will be established by or pursuant to a resolution of our board of directors, or a committee thereof, and set forth or determined in the manner provided in an officer's certificate or by a supplemental indenture. The particular terms of each series of debt securities will be described in a prospectus supplement relating to such series, including any pricing supplement.

We can issue an unlimited amount of debt securities under the indenture that may be in one or more series with the same or various maturities, at par, at a premium or at a discount. We will set forth in a prospectus supplement, including any pricing supplement, relating to any series of debt securities being offered, the aggregate principal amount and the following terms of the debt securities:

- the title of the debt securities;
- the price or prices (expressed as a percentage of the principal amount) at which we will sell the debt securities;
- any limit on the aggregate principal amount of the debt securities;
- the date or dates on which we will pay the principal on the debt securities;
- the rate or rates (which may be fixed or variable) per annum or the method used to determine the rate or rates (including any commodity, commodity index, stock exchange index or financial index) at which the debt securities will bear interest, the date or dates from which interest will accrue, the date or dates on which interest will commence and be payable and any regular record date for the interest payable on any interest payment date;
- the place or places where principal of, and interest, if any, on, the debt securities will be payable;
- the terms and conditions upon which we may redeem the debt securities;
- any obligation we have to redeem or purchase the debt securities pursuant to any sinking fund or analogous provisions or at the option of a holder of debt securities;

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- the dates on which and the price or prices at which we will repurchase debt securities at the option of the holders of debt securities and other detailed terms and provisions of these repurchase obligations;
- the denominations in which the debt securities will be issued, if other than denominations of \$1,000 and any integral multiple thereof;
- whether the debt securities will be issued in the form of certificated debt securities or global debt securities;
- the portion of principal amount of the debt securities payable upon declaration of acceleration of the maturity date, if other than the principal amount;
- the currency of denomination of the debt securities;
- the designation of the currency, currencies or currency units in which payment of principal of, and premium and interest on, the debt securities will be made;
- if payments of principal of, or premium or interest on, the debt securities will be made in one or more currencies or currency units other than that or those in which the debt securities are denominated, the manner in which the exchange rate with respect to these payments will be determined;
- the manner in which the amounts of payment of principal of, or premium or interest on, the debt securities will be determined, if these amounts may be determined by reference to an index based on a currency or currencies other than that in which the debt securities are denominated or designated to be payable or by reference to a commodity, commodity index, stock exchange index or financial index;
- any provisions relating to any security provided for the debt securities;
- any addition to or change in the events of default described in this prospectus or in the indenture with respect to the debt securities and any change in the acceleration provisions described in this prospectus or in the indenture with respect to the debt securities;
- any addition to or change in the covenants described in this prospectus or in the indenture with respect to the debt securities;
- any conversion provisions, including the conversion price, the conversion period, provisions as to whether conversion will be mandatory, at the option of the holder or at our option, the events requiring an adjustment of the conversion price and provisions affecting conversion if such series of debt securities are redeemed;
- whether the debt securities will be senior debt securities or subordinated debt securities and, if applicable, a description of the subordination terms thereof;
- any depositaries, interest rate calculation agents, exchange rate calculation agents or other agents with respect to the debt securities; and
- any other terms of the debt securities, which may modify, delete, supplement or add to any provision of the indenture as it applies to that series.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

If we denominate the purchase price of any of the debt securities in a foreign currency or currencies or a foreign currency unit or units, or if the principal of, and premium and interest on, any series of debt securities is payable in a foreign currency or currencies or a foreign currency unit or units, we will provide you with information on the restrictions, elections, general tax considerations, specific terms and other information with

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respect to that issue of debt securities and such foreign currency or currencies or foreign currency unit or units in the applicable prospectus supplement.

Transfer and Exchange

Each debt security will be represented by either one or more global securities registered in the name of The Depository Trust Company, as Depository, or a nominee (we will refer to any debt security represented by a global debt security as a “book-entry debt security”), or a certificate issued in definitive registered form (we will refer to any debt security represented by a certificated security as a “certificated debt security”) as set forth in the applicable prospectus supplement. Except as set forth under the heading “Legal Ownership of Securities” below, book-entry securities will not be issuable in certificated form.

You may transfer or exchange certificated debt securities at any office we maintain for this purpose in accordance with the terms of the indenture. No service charge will be made for any transfer or exchange of certificated debt securities, but we may require payment of a sum sufficient to cover any tax or other governmental charge payable in connection with a transfer or exchange.

You may effect the transfer of certificated debt securities and the right to receive the principal of, and any premium and interest on, certificated debt securities only by surrendering the certificate representing those certificated debt securities and either reissuance by us or the trustee of the certificate to the new holder or the issuance by us or the trustee of a new certificate to the new holder.

No Protection in the Event of a Change of Control

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions which may afford holders of the debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control) which could adversely affect holders of debt securities.

Covenants

We will set forth in the applicable prospectus supplement any restrictive covenants applicable to any issue of debt securities.

Consolidation, Merger and Sale of Assets

We may not consolidate with or merge with or into, or convey, transfer or lease all or substantially all of our properties and assets to, any person, which we refer to as a successor person, unless:

- we are the surviving corporation or the successor person (if other than Lexicon) is organized and validly existing under the laws of any U.S. domestic jurisdiction and expressly assumes our obligations on the debt securities and under the indenture;
- immediately after giving effect to the transaction, no event of default, and no event which, after notice or lapse of time, or both, would become an event of default, shall have occurred and be continuing under the indenture; and
- certain other conditions are met.

Events of Default

Event of default means, with respect to any series of debt securities, any of the following:

- default in the payment of any interest upon any debt security of that series when it becomes due and payable, and continuance of that default for a period of 30 days (unless the entire amount of the payment is deposited by us with the trustee or with a paying agent prior to the expiration of the 30-day period);

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- default in the payment of principal of or premium on any debt security of that series when due and payable;
- default in the deposit of any sinking fund payment, when and as due in respect of any debt security of that series;
- default in the performance or breach of any other covenant or warranty by us in the indenture (other than a covenant or warranty that has been included in the indenture solely for the benefit of a series of debt securities other than that series), which default continues uncured for a period of 90 days after we receive written notice from the trustee or we and the trustee receive written notice from the holders of not less than a majority in principal amount of the outstanding debt securities of that series as provided in the indenture;
- certain events of bankruptcy, insolvency or reorganization of our company; and
- any other event of default provided with respect to debt securities of that series that is described in the applicable prospectus supplement accompanying this prospectus.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an event of default with respect to any other series of debt securities. The occurrence of an event of default may constitute an event of default under our bank credit agreements in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

If an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) of, and accrued and unpaid interest, if any, on all debt securities of that series. In the case of an event of default resulting from certain events of bankruptcy, insolvency or reorganization, the principal (or such specified amount) of and accrued and unpaid interest, if any, on all outstanding debt securities will become and be immediately due and payable without any declaration or other act on the part of the trustee or any holder of outstanding debt securities. At any time after a declaration of acceleration with respect to debt securities of any series has been made, but before a judgment or decree for payment of the money due has been obtained by the trustee, the holders of a majority in principal amount of the outstanding debt securities of that series may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the indenture. We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an event of default.

The indenture provides that the trustee will be under no obligation to exercise any of its rights or powers under the indenture at the request of any holder of outstanding debt securities, unless the trustee receives indemnity satisfactory to it against any loss, liability or expense. Subject to certain rights of the trustee, the holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to the debt securities of that series.

No holder of any debt security of any series will have any right to institute any proceeding, judicial or otherwise, with respect to the indenture or for the appointment of a receiver or trustee, or for any remedy under the indenture, unless:

- that holder has previously given to the trustee written notice of a continuing event of default with respect to debt securities of that series; and

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- the holders of at least a majority in principal amount of the outstanding debt securities of that series have made written request, and offered reasonable indemnity, to the trustee to institute the proceeding as trustee, and the trustee has not received from the holders of a majority in principal amount of the outstanding debt securities of that series a direction inconsistent with that request and has failed to institute the proceeding within 60 days.

Notwithstanding the foregoing, the holder of any debt security will have an absolute and unconditional right to receive payment of the principal of, and any premium and interest on, that debt security on or after the due dates expressed in that debt security and to institute suit for the enforcement of payment.

If any securities are outstanding under the indenture, the indenture requires us, within 120 days after the end of our fiscal year, to furnish to the trustee a statement as to compliance with the indenture. The indenture provides that the trustee may withhold notice to the holders of debt securities of any series of any default or event of default (except in payment on any debt securities of that series) with respect to debt securities of that series if it in good faith determines that withholding notice is in the interest of the holders of those debt securities.

Modification and Waiver

We may modify and amend the indenture with the consent of the holders of at least a majority in principal amount of the outstanding debt securities of each series affected by the modifications or amendments. We may not make any modification or amendment without the consent of the holders of each affected debt security then outstanding if that amendment will:

- reduce the amount of debt securities whose holders must consent to an amendment or waiver;
- reduce the rate of or extend the time for payment of interest (including default interest) on any debt security;
- reduce the principal of or premium on or change the fixed maturity of any debt security or reduce the amount of, or postpone the date fixed for, the payment of any sinking fund or analogous obligation with respect to any series of debt securities;
- reduce the principal amount of discount securities payable upon acceleration of maturity;
- waive a default in the payment of the principal of, or premium or interest on, any debt security (except a rescission of acceleration of the debt securities of any series by the holders of at least a majority in aggregate principal amount of the then outstanding debt securities of that series and a waiver of the payment default that resulted from such acceleration);
- make the principal of, or premium or interest on, any debt security payable in currency other than that stated in the debt security;
- make any change to certain provisions of the indenture relating to, among other things, the right of holders of debt securities to receive payment of the principal of, and premium and interest on, those debt securities and to institute suit for the enforcement of any such payment and to waivers or amendments; or
- waive a redemption payment with respect to any debt security.

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, or any premium or interest on, any debt security of that series or in respect of a covenant or provision, which cannot be modified or amended without the consent of the holder of each outstanding debt

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security of the series affected; *provided, however*, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

Discharge of Indenture

The indenture provides that, unless otherwise provided by the terms of the applicable series of debt securities, we may be discharged from any and all obligations in respect of the debt securities of any series (except for certain obligations to register the transfer or exchange of debt securities of such series, to replace stolen, lost or mutilated debt securities of such series, and to maintain paying agencies and certain provisions relating to the treatment of funds held by paying agents). We will be so discharged upon satisfying the requirements in the indenture, including the deposit with the trustee, in trust, of money and/or U.S. government obligations or, in the case of debt securities denominated in a single currency other than U.S. dollars, foreign government obligations, that, through the payment of interest and principal in accordance with their terms, will provide money in an amount sufficient in the opinion of a nationally recognized firm of independent public accountants to pay and discharge each installment of principal of, premium and interest on and any mandatory sinking fund payments in respect of the debt securities of that series on the stated maturity of those payments in accordance with the terms of the indenture and those debt securities.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the laws of the State of New York.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants that we may offer in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report filed under the Exchange Act.

General

We will describe in the applicable prospectus supplement the terms of the series of warrants, including:

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- if applicable, the date on and after which the warrants and the related securities will be separately transferable;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;
- the terms of any rights to redeem or call the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreements and warrants may be modified;
- federal income tax consequences of holding or exercising the warrants;
- the terms of the securities issuable upon exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable upon such exercise, including:

- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any; or

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- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants at any time up to the specified time on the expiration date that we set forth in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

Holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to the warrant agent in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to the warrant agent.

Upon receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent or any other office indicated in the applicable prospectus supplement, we will issue and deliver the securities purchasable upon such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Governing Law

The warrants and warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable upon exercise of, its warrants.

DESCRIPTION OF RIGHTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the rights that we may offer under this prospectus and the related rights agreements. While the terms summarized below will apply generally to any rights that we may offer under this prospectus, we will describe the particular terms of any series of rights that we may offer in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any rights offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. Specific rights agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report filed under the Exchange Act.

General

We may issue rights to purchase common stock, preferred stock, debt securities or other securities. These rights may be issued independently or together with any other security offered hereby and may or may not be transferable by the stockholder receiving the rights in such offering. In connection with any offering of such rights, we may enter into a standby arrangement with one or more underwriters or other purchasers pursuant to which the underwriters or other purchasers may be required to purchase any securities remaining unsubscribed for after such offering.

Each series of rights will be issued under a separate rights agreement which we will enter into with a bank or trust company, as rights agent, all as set forth in the applicable prospectus supplement. The rights agent will act solely as our agent in connection with the certificates relating to the rights and will not assume any obligation or relationship of agency or trust with any holders of rights certificates or beneficial owners of rights. We will file the rights agreement and the rights certificates relating to each series of rights with the SEC, and incorporate them by reference as an exhibit to the registration statement of which this prospectus is a part on or before the time we issue a series of rights.

We will describe in the applicable prospectus supplement the terms of the series of rights, including:

- the date of determining the stockholders entitled to the rights distribution;
- the number of rights issued or to be issued to each stockholder;
- the exercise price payable for each share of common stock, preferred stock, debt securities or other securities upon the exercise of the rights;
- the number and terms of the shares of common stock, preferred stock, debt securities or other securities which may be purchased per each right;
- the extent to which the rights are transferable, if at all;
- the date on which the holder's ability to exercise the rights shall commence, and the date on which the rights shall expire;
- the extent to which the rights may include an over-subscription privilege with respect to unsubscribed securities;
- if applicable, the material terms of any standby underwriting or purchase arrangement entered into by us in connection with the offering of such rights; and
- any other terms of the rights, including the terms, procedures, conditions and limitations relating to the exchange and exercise of the rights.

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The description in the applicable prospectus supplement of any rights that we may offer will not necessarily be complete and will be qualified in its entirety by reference to the applicable rights certificate, which will be filed with the SEC.

Exercise of Rights

Each right will entitle the holder of the right to purchase for cash such amount of shares of common stock, preferred stock, debt securities or other securities at such exercise price as shall in each case be set forth in, or be determinable as set forth in, the prospectus supplement relating to the rights offered thereby. Rights may be exercised at any time up to the close of business on the expiration date for such rights set forth in the prospectus supplement. After the close of business on the expiration date, all unexercised rights will become void.

Rights may be exercised as set forth in the prospectus supplement relating to the rights offered thereby. Upon receipt of payment and the rights certificate properly completed and duly executed at the corporate trust office of the rights agent or any other office indicated in the prospectus supplement, we will forward, as soon as practicable, the shares of common stock, preferred stock, debt securities or other securities purchasable upon such exercise. We may determine to offer any unsubscribed offered securities directly to persons other than stockholders, to or through agents, underwriters or dealers or through a combination of such methods, including pursuant to standby underwriting arrangements, as set forth in the applicable prospectus supplement.

Governing Law

The rights and rights agreements will be governed by and construed in accordance with the laws of the State of New York.

DESCRIPTION OF UNITS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the units that we may offer under this prospectus and the related unit agreements. While the terms summarized below will apply generally to any units that we may offer under this prospectus, we will describe the particular terms of any series of units that we may offer in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any units offered under that prospectus supplement may differ from the terms described below. However, no prospectus supplement shall fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness. Specific unit agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus or as an exhibit to a report filed under the Exchange Act.

General

We may issue units comprised of one or more shares of common stock, shares of preferred stock, debt securities and warrants in any combination. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date.

We will describe in the applicable prospectus supplement the terms of the series of units, including:

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement that differ from those described below; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

The provisions described in this section, as well as those described under “Description of Capital Stock,” “Description of Debt Securities” and “Description of Warrants” will apply to each unit and to any common stock, preferred stock, debt security or warrant included in each unit, respectively.

Issuance in Series

We may issue units in such amounts and in numerous distinct series as we determine.

Enforceability of Rights by Holders of Units

Each unit agent will act solely as our agent under the applicable unit agreement and will not assume any obligation or relationship of agency or trust with any holder of any unit. A single bank or trust company may act as unit agent for more than one series of units. A unit agent will have no duty or responsibility in case of any default by us under the applicable unit agreement or unit, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a unit may, without the consent of the related unit agent or the holder of any other unit, enforce by appropriate legal action its rights as holder under any security included in the unit.

Title

Lexicon, the unit agents and any of their agents may treat the registered holder of any unit certificate as an absolute owner of the units evidenced by that certificate for any purpose and as the person entitled to exercise the rights attaching to the units so requested, despite any notice to the contrary. See “Legal Ownership of Securities.”

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee maintain for this purpose as the “holders” of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as “indirect holders” of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary’s book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its nominee. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a book-entry security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary’s book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in “street name.” Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

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For example, once we make a payment or give a notice to the holder, we have no further responsibility for the payment or notice even if that holder is required, under agreements with depository participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the holders contact the indirect holders is up to the holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form or in street name, you should check with your own institution to find out:

- how it handles securities payments and notices;
- whether it imposes fees or charges;
- how it would handle a request for the holders' consent, if ever required;
- whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;
- how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and
- if the securities are in book-entry form, how the depository's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depository. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depository. Unless we specify otherwise in the applicable prospectus supplement, The Depository Trust Company, New York, New York, known as DTC, will be the depository for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depository, its nominee or a successor depository, unless special termination situations arise. We describe those situations below under "Special Situations When a Global Security Will Be Terminated." As a result of these arrangements, the depository, or its nominee, will be the sole registered owner and holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depository or with another institution that does. Thus, an investor whose security is represented by a global security will not be a holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations for Global Securities

As an indirect holder, an investor's rights relating to a global security will be governed by the account rules of the investor's financial institution and of the depository, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depository that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

- An investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;
- An investor will be an indirect holder and must look to his or her own bank or broker for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;
- An investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;
- An investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;
- The depository's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security. We and any applicable trustee have no responsibility for any aspect of the depository's actions or for its records of ownership interests in a global security. We and the trustee also do not supervise the depository in any way;
- The depository may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and
- Financial institutions that participate in the depository's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities. There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

The global security will terminate when the following special situations occur:

- if the depository notifies us that it is unwilling, unable or no longer qualified to continue as depository for that global security and we do not appoint another institution to act as depository within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or
- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

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The prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the prospectus supplement. When a global security terminates, the depositary, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference into this prospectus contain certain information regarding our financial projections, plans and strategies that are forward-looking statements. We have attempted to identify forward-looking statements by terminology including “anticipate,” “believe,” “can,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “should” or “will” or the negative of these terms or other comparable terminology. These statements, which are only predictions and involve known and unknown risks, uncertainties and other important factors may include, among other things, statements which address our strategy and operating performance, events or developments that we expect or anticipate will occur in the future, such as projections of our future results of operations or of our financial condition, the regulatory status and therapeutic and commercial potential of our drug programs, the status of any collaborative agreements or clinical trials, the expected timing of the completion of our ongoing and future clinical trials and the results of such trials, including top-line data, expected timing of initiation of our planned clinical trials, expected enrollment in our ongoing and future clinical trials, and our research and development efforts and anticipated trends in our business.

We have based these forward-looking statements on our current expectations and projections about future events. However, there may be events in the future that we are not able to predict accurately or which we do not fully control that could cause actual results to differ materially from those expressed or implied in our forward-looking statements. Many important factors could cause actual results to differ materially from those expressed or implied by these forward-looking statements, including those discussed under “Risk Factors” in this prospectus and any prospectus supplement and other sections of the documents incorporated by reference into this prospectus. As a result, you should not rely on such statements in making your investment decision. Except as required by applicable law, we undertake no obligation to publicly release any revisions to the forward-looking statements or reflect events or circumstances after the date of this prospectus.

USE OF PROCEEDS

Except as otherwise described in the prospectus supplement relating to an offering, we intend to use the net proceeds from the sale(s) of securities offered pursuant to this prospectus and any prospectus supplement for research, development and commercialization activities and other general corporate purposes, including capital expenditures and working capital needs. We may also use some or all of the net proceeds to acquire or invest in businesses, products and technologies that are complementary to our own.

The amounts that we actually expend for working capital purposes, investments or acquisitions will vary significantly depending on a number of factors, including our future revenues, the amount of cash we generate from operations and the progress of our research, development and commercialization efforts. Accordingly, our management will retain broad discretion in the allocation of the net proceeds from the sale(s) of the offered securities. If we elect at the time of the issuance of the securities to make different or more specific use of proceeds other than as described in this prospectus, the change in use of proceeds will be described in the applicable prospectus supplement.

PLAN OF DISTRIBUTION

We may sell securities under this prospectus from time to time in any one or more of the following ways:

- to or through underwriters;
- through brokers or dealers;
- directly to other purchasers; or
- through agents.

We may sell securities under this prospectus from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at varying prices determined at the time of sale;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

The prospectus supplement relating to the securities will set forth the terms of the offering of such securities, including the name or names of any underwriters, brokers, dealers or agents, the name or names of any managing underwriter or underwriters, the purchase price of the securities and the net proceeds to us from such sale, any delayed delivery arrangements, any underwriting discounts and commissions and other items constituting underwriters' compensation, any public offering price, any discounts or concessions allowed or reallocated or paid to dealers, any commissions paid to agents and any securities exchange or market on which the securities may be listed.

If we use underwriters in the sale of securities, the underwriters will acquire the securities for their own account. The underwriters may resell the securities from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. Underwriters may offer securities to the public either through underwriting syndicates represented by one or more managing underwriters or directly by one or more firms acting as underwriters. Unless we inform you otherwise in the prospectus supplement, the obligations of the underwriters to purchase the securities will be subject to certain conditions, and the underwriters will be obligated to purchase all of the offered securities if they purchase any of them. The underwriters may change from time to time any public offering price and any discounts or concessions allowed or reallocated or paid to dealers.

In connection with the sale of our securities, underwriters, brokers, dealers or agents may receive compensation from us or purchasers of securities for whom they may act as agents, in the form of discounts, concessions or commissions. Underwriters, dealers and agents that participate in the distribution of our securities may be deemed to be underwriters, and any discounts or commissions received by them from us and any profit on the resale of securities by them may be deemed to be underwriting discounts and commissions under the Securities Act of 1933, or the Securities Act. Any person who may be deemed to be an underwriter will be identified, and the compensation received from us will be described, in the prospectus supplement.

During and after an offering through underwriters, the underwriters may purchase and sell the securities in the open market. These transactions may include over-allotment and stabilizing transactions and purchases to cover syndicate short positions created in connection with the offering. The underwriters may also impose a penalty bid, whereby selling concessions allowed to syndicate members or other broker-dealers for the securities sold for their account may be reclaimed by the syndicate if those securities are repurchased by the syndicate in stabilizing or covering transactions. These activities may stabilize, maintain or otherwise affect the market price of the securities, which may be higher than the price that might otherwise prevail in the open market, and, if commenced, may be discontinued at any time.

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If dealers or brokers acting as dealers are used in the sale of the securities, we will sell the securities to such dealers or brokers as principals. The dealers or brokers acting as dealers may then resell such securities to the public at varying prices to be determined by such dealers or brokers at the time of resale. The names of dealers or brokers acting as dealers and the terms of the transaction will be set forth in the prospectus supplement relating to such securities. We may sell the securities directly or through agents designated by us from time to time. Any agent involved in the offer or sale of the securities will be named, and any commissions that we pay to such agent will be set forth, in the prospectus supplement relating to such securities. Unless otherwise indicated in the prospectus supplement, any such agent will be acting on a best efforts basis for the period of its appointment.

We may sell securities directly, in which case no underwriters or agents would be involved. We may sell securities directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act with respect to any sale of those securities.

We may offer securities through agents in connection with a distribution to our stockholders of rights to purchase such securities. The terms of any such sales will be described in the prospectus supplement relating thereto. Pursuant to any standby underwriting agreement entered into in connection with a rights offering to our stockholders, persons acting as standby underwriters may receive a commitment fee for all securities underlying the rights that the underwriter commits to purchase on a standby basis. Additionally, prior to the expiration date with respect to any rights, any standby underwriters in a rights offering to our stockholders may offer such securities on a when-issued basis, including securities to be acquired through the purchase and exercise of rights, at prices set from time to time by the standby underwriters. After the expiration date with respect to such rights, the underwriters may offer securities of the type underlying the rights, whether acquired pursuant to a standby underwriting agreement, the exercise of the rights or the purchase of such securities in the market, to the public at a price or prices to be determined by the underwriters. The standby underwriters may thus realize profits or losses independent of the underwriting discounts or commissions paid by us. If we do not enter into a standby underwriting agreement in connection with a rights offering to our stockholders, we may elect to retain a dealer-manager to manage such a rights offering for us. We also may enter into a standby arrangement with other purchasers pursuant to which such purchasers may be required to purchase any securities remaining unsubscribed for after such offering. Any such dealer-manager may offer securities of the type underlying the rights acquired or to be acquired pursuant to the purchase and exercise of rights and may thus realize profits or losses independent of any dealer-manager fee paid by us.

All securities we offer, other than common stock and other securities issued upon a reopening of a previous series, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

If so indicated in the prospectus supplement, we will authorize agents, underwriters, brokers or dealers to solicit offers from certain types of institutions to purchase securities at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. Such contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth also the commission payable for solicitation of such contracts.

We may have agreements with the underwriters, dealers and agents to indemnify them against specific civil liabilities, including liabilities under the Securities Act, or to contribute with respect to payments which the underwriters, dealers or agents may be required to make as a result of those specific civil liabilities.

Underwriters and agents and their affiliates may be customers of, engage in transactions with, or perform services for us or our subsidiaries in the ordinary course of their businesses.

LEGAL MATTERS

The validity of the issuance of the securities offered by this prospectus has been passed upon for us by Vinson & Elkins L.L.P., Houston, Texas.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our annual report on Form 10-K for the year ended December 31, 2020, and the effectiveness of our internal control over financial reporting as of December 31, 2020, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy the reports, proxy statements and other information that we file with the SEC at 100 F Street, NE, Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for information and for its prescribed rates to obtain copies of such material. The SEC also maintains a website that contains reports, proxy and information statements and other information regarding registrants, like us, that file electronically with the SEC. The address of the SEC's Internet site is www.sec.gov.

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and other filings with the SEC are available, free of charge, through our website, as soon as reasonably practicable after those reports or filings are electronically filed with or furnished to the SEC. Information on our website or any other website is not incorporated by reference into this prospectus or any prospectus supplement and does not constitute a part of this prospectus or any prospectus supplement.

This prospectus is part of a registration statement we filed with the SEC relating to the securities we may offer. As permitted by SEC rules, this prospectus does not contain all of the information we have included in the registration statement and the accompanying exhibits and schedules we filed with the SEC. You should refer to the registration statement, exhibits and schedules for more information about us and the securities. The registration statements, exhibits and schedules are available at the SEC or through its website.

DOCUMENTS INCORPORATED BY REFERENCE

The SEC allows us to "incorporate by reference" the information we have filed with it, which means that we can disclose important information to you by referring you to those documents. The information we incorporate by reference is an important part of this prospectus, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below that we have previously filed with the SEC and any future documents filed with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act subsequent to the date of this prospectus and prior to the termination of the offering of the securities covered by this prospectus:

- our annual report on [Form 10-K](#) for the year ended December 31, 2020;
- our quarterly reports on Form 10-Q for the quarterly periods ended [March 31](#) and [June 30, 2021](#);
- our current reports on Form 8-K dated [January 14](#), [February 8](#), [March 29](#), [April 29](#) and [July 28, 2021](#); and

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- the description of our common stock contained in our registration statement on [Form 8-A](#) filed with the SEC on March 27, 2000 pursuant to Section 12 of the Exchange Act, including any amendments and reports filed for the purpose of updating such description.

Any statement contained in a document incorporated or deemed to be incorporated by reference in this prospectus will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or in any other subsequently filed document which also is or is deemed to be incorporated by reference in this prospectus modifies or supersedes that statement. Any statement that is modified or superseded will not constitute a part of this prospectus, except as so modified or superseded. You may rely on any statement contained in this prospectus or in documents incorporated or deemed to be incorporated in this prospectus, unless that statement has been subsequently modified or superseded as described above prior to the time you make your investment decision.

Upon your written or oral request, we will provide you at no cost a copy of any or all of the documents incorporated by reference in this prospectus, other than the exhibits to those documents, unless the exhibits are specifically incorporated by reference into this prospectus. You may request a copy of these documents by contacting:

Investor Relations
Lexicon Pharmaceuticals, Inc.
2445 Technology Forest Blvd., 11th Floor
The Woodlands, Texas 77381-1160
Telephone: (281) 863-3000

Shares

Lexicon Pharmaceuticals, Inc.

Common Stock



PRELIMINARY PROSPECTUS SUPPLEMENT

, 2023

Citigroup

Jefferies

Piper Sandler
