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LEXICON PHARMACEUTICALS, INC./DE Form POS AM August 15, 2011

AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON AUGUST 12, 2011

Registration No. 333-171953

UNITED STATES SECURITIES AND EXCHANGE COMMISSION Washington, D.C. 20549 Post-Effective Amendment No. 2 to Form S-3 on FORM S-1 **REGISTRATION STATEMENT** UNDER THE SECURITIES ACT OF 1933 Lexicon Pharmaceuticals, Inc. (Exact name of registrant as specified in its charter) 76-0474169 Delaware 2834 (State or other jurisdiction of (I.R.S. Employer (Primary Standard Industrial incorporation or organization) Classification Code Number) Identification Number)

8800 Technology Forest Place The Woodlands, Texas 77381-1160 (281) 863-3000 (Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Arthur T. Sands, M.D., Ph.D. President and Chief Executive Officer 8800 Technology Forest Place The Woodlands, Texas 77381-1160 (281) 863-3000 (Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Brian T. Crum David P. Oelman Vice President and General Counsel Vinson & Elkins L.L.P. Lexicon Pharmaceuticals, Inc. 1001 Fannin, Suite 2500 8800 Technology Forest Place Houston, Texas 77002-6760 The Woodlands, Texas 77381-1160 (713) 758-2222

Approximate date of commencement of proposed sale to the public:

As soon as practicable after the effective date of this registration statement.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. o

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same

(281) 863-3000

offering. o

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Large accelerated filer o Accelerated filer x Non-accelerated filer (Do not check if a smaller reporting company) o Smaller reporting company o

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered	Proposed Maximum Offering Price Per Unit (2) (3)	Offering Price	Amount of Registration Fee
Common Stock, par value \$0.001	(1)	(1)	\$200,000,000 (1) (2)	\$23,220 (3)
Rights to purchase Common Stock (4)		N/A	N/A	N/A

(1) Estimated solely for the purpose of calculating the registration fee in accordance with Rule 457 under the Securities Act.

(2) Represents the aggregate gross proceeds from the issuance of the maximum number of shares of common stock which may be issued pursuant to the exercise of rights.

(3) The registration fee was previously paid in connection with the filing of the original registration statement on Form S-3 on January 28, 2011.

(4) Evidencing the rights to subscribe for shares of common stock. Pursuant to Rule 457(g) under the Securities Act, no separate registration fee is required for the rights because the rights are being registered in the same registration statement as the common stock of the registrant underlying the rights.

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED AUGUST 12, 2011 Lexicon Pharmaceuticals, Inc. Shares Common Stock

We are distributing, at no charge, to holders of our common stock non-transferable subscription rights to purchase up to shares of our common stock. We refer to this offering as the "rights offering." In the rights offering, you will receive one subscription right for every share of common stock you owned at 5:00 p.m., New York time, on [•], 2011, the record date.

Each whole subscription right will entitle you to purchase shares of our common stock at a subscription price of \$[•] per share, which we refer to as the "basic subscription privilege." We will not issue fractional shares of common stock in the rights offering, and holders will only be entitled to purchase a whole number of shares of common stock, rounded down to the nearest whole number a holder would otherwise be entitled to purchase. If you exercise your rights in full, you may also exercise an over-subscription right to purchase additional shares that remain unsubscribed at the expiration of the rights offering, subject to availability and certain other limitations, which we refer to as the "over-subscription privilege."

We are conducting the rights offering at the election of two of our largest stockholders, Invus, L.P. and Invus C.V., which we refer to collectively as "Invus," pursuant to their contractual rights to require us to initiate a pro rata rights offering to our stockholders. Invus is required to exercise its basic subscription privilege in full and purchase at least shares of our common stock in the rights offering.

The subscription rights may not be transferred or sold. The subscription rights will expire and will be void and worthless if they are not exercised by 5:00 p.m., New York time, on [•], 2011, unless we and Invus agree to extend the rights offering period. We reserve the right to cancel the rights offering at any time, for any reason, with Invus' consent.

You should carefully consider whether to exercise your subscription rights before the expiration of the rights offering. All exercises of subscription rights are irrevocable. If you do not exercise your basic subscription privilege in full, you will own, upon completion of the rights offering, a smaller proportional interest in our common stock than otherwise would be the case if you had fully exercised your rights.

We have engaged BNY Mellon Shareowner Services to serve as the subscription agent for the rights offering. The subscription agent will hold in escrow the funds we receive from subscribers until we complete or cancel the rights offering. This is not an underwritten offering. The shares are being offered directly by us without the services of an underwriter or selling agent. BNY Mellon also will serve as information agent for the rights offering.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "LXRX." On [•], 2011, the last reported sale price of our common stock on the Nasdaq Global Select Market was \$[•] per share.

Exercising your subscription rights and investing in our common stock involves risks. See "Risk Factors" beginning on page 14 of this prospectus.

	Per Share	Aggregate
Subscription Price	\$[•]	\$[•]
Estimated Expenses	\$[•]	\$[•]
Net Proceeds to Us	\$[•]	\$[•]

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved these securities or passed upon the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal

offense.

, 2011

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You should rely only on the information contained in this prospectus and 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. 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.

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, LexVision[®] and OmniBank[®] are registered trademarks and Genome5000Ths a trademark of Lexicon Pharmaceuticals, Inc.

PROSPECTUS SUMMARY

This summary does not contain all of the information that you should consider before exercising your subscription rights and investing in our common stock. You should read this entire prospectus carefully, including the section entitled "Risk Factors" and the financial statements and related notes and other information incorporated by reference in this prospectus, before making an investment decision.

LEXICON PHARMACEUTICALS, INC.

Lexicon Pharmaceuticals, Inc. is a biopharmaceutical company focused on the discovery and development of breakthrough treatments for human disease. We have used our proprietary gene knockout technology 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. For targets that we believe have high pharmaceutical value, we engage in programs for the discovery and development of potential new drugs.

We have four drug candidates for which we have completed Phase 2 clinical trials:

We have completed a Phase 2a clinical trial and are presently conducting a Phase 2b clinical trial of LX4211, an orally-delivered small molecule compound that we are developing as a treatment for type 2 diabetes;

We have completed a Phase 2a clinical trial of LX1031, an orally-delivered small molecule compound that we are developing as a treatment for irritable bowel syndrome and other gastrointestinal disorders, and Phase 1 clinical trials of LX1033, a more potent back-up molecule that we plan to advance into Phase 2 clinical trials;

We have completed a Phase 2a clinical trial and are presently conducting an additional Phase 2 clinical trial of LX1032, an orally-delivered small molecule compound that we are developing as a treatment for the symptoms associated with carcinoid syndrome; and

We have completed a Phase 2a clinical trial and plan to conduct a dose-ranging study to explore higher doses of LX2931, an orally-delivered small molecule compound that we are developing as a treatment for rheumatoid arthritis and other autoimmune diseases.

We have also advanced three other drug candidates into preclinical development: LX7101, a topically-delivered small molecule compound that we are developing as a treatment for glaucoma; LX5061, an orally-delivered small molecule compound that we are developing as a treatment for osteoporosis; and LX2311, an orally-delivered small molecule compound that we are developing as a treatment for autoimmune diseases. We have small molecule compounds from a number of additional drug discovery programs in various stages of preclinical research and believe that our systematic, target biology-driven approach to drug discovery will enable us to continue to expand our clinical pipeline.

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We are working both independently and through strategic collaborations and alliances to capitalize on our technology, drug target discoveries and drug discovery and development programs. Consistent with this approach, we seek to retain exclusive rights to the benefits of certain of our small molecule drug programs by developing drug candidates from those programs internally and to collaborate with third parties with respect to the discovery, development and commercialization of small molecule and biotherapeutic drug candidates for other targets, particularly when the collaboration provides us with access to expertise and resources that we do not possess internally or are complementary to our own. We have established drug discovery and development collaborations with a number of leading pharmaceutical and biotechnology companies which generated near-term cash while offering us the potential to retain economic participation in products our collaborators develop through the collaboration. In addition, we have established collaborations and license agreements with other leading pharmaceutical and biotechnology companies, research institutes and academic institutions under which we received fees and, in some cases, are eligible to receive milestone and royalty payments, in return for granting access to some of our technologies and discoveries.

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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, or 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, or SEC. Information found on our website is not incorporated by reference into this prospectus and should not be considered part of this document.

Lexicon Pharmaceuticals, Inc. was incorporated in Delaware in July 1995, and commenced operations in September 1995. Our corporate headquarters are located at 8800 Technology Forest Place, The 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."

THE RIGHTS OFFERING