

LEXICON PHARMACEUTICALS, INC./DE
Form POS AM
May 26, 2011

AS FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON MAY 26, 2011

Registration No. 333-171953

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Post-Effective Amendment No. 1
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)

Delaware

2,834

76-0474169

(State or other jurisdiction of
incorporation or organization)

(Primary Standard Industrial
Classification Code Number)

(I.R.S. Employer
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)

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Vice President and General Counsel

Lexicon Pharmaceuticals, Inc.

8800 Technology Forest Place

The Woodlands, Texas 77381-1160

(281) 863-3000

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. "

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. "

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 offering. "

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. "

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 Accelerated filer Non-accelerated filer (Do not check if a smaller reporting company) Smaller reporting company "

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.

EXPLANATORY NOTE

We initially registered on a registration statement on Form S-3 (File No. 333-171953) the offer and sale of 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. The registration statement also registered the issuance of 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.

Due to late filing of disclosure required under Item 9.01 of Form 8-K, under applicable Securities and Exchange Commission rules we do not currently qualify for the use of a registration statement on Form S-3. This post-effective amendment No. 1 on Form S-1 is being filed to convert such registration statement on Form S-3 into a registration statement on Form S-1 registering the offer and sale of common stock. All filing fees payable in connection with the registration of the offer and sale of such common stock were previously paid in connection with the filing of the original registration statement on Form S-3.

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 MAY 26, 2011

Lexicon Pharmaceuticals, Inc.

Common Stock

Lexicon is offering shares of its common stock. Of these shares, _____ are being offered through the underwriters named in the prospectus and _____ are being offered by Lexicon directly to Invus, L.P. and Invus C.V., two of Lexicon's largest stockholders. If Invus elects to purchase these shares, it will purchase directly from Lexicon at the price to the public.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "LXRX." On May 25, 2011, the reported last sale price of our common stock on The Nasdaq Global Select Market was \$1.46 per share.

Investing in our common stock involves risks. See "Risk Factors" beginning on page 6 of this prospectus.

PRICE \$ _____ A SHARE

Per Share	Price to Public	Underwriting Discounts and Commissions	Proceeds to Lexicon Pharmaceuticals
Total	\$ _____	\$ _____	\$ _____

The underwriters will not receive any compensation with respect to the shares being offered by Lexicon to Invus. We have granted the underwriters the right to purchase up to an additional _____ shares to cover over-allotments. The Securities and Exchange Commission and state securities regulators have not approved or disapproved these securities, or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares to purchasers on _____, 2011.

_____, 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 is 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 Genome5000™ is a trademark of Lexicon Pharmaceuticals, Inc.

PROSPECTUS SUMMARY

This summary does not contain all of the information that you should consider before investing in our common stock. You should read this entire prospectus carefully, including the “Risk Factors” section of this prospectus beginning on page 6 and the financial statements 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 or are presently conducting Phase 2 clinical trials:

LX4211, an orally-delivered small molecule compound that we are developing as a treatment for type 2 diabetes;

LX1031, an orally-delivered small molecule compound that we are developing as a treatment for irritable bowel syndrome and other gastrointestinal disorders;

LX1032, an orally-delivered small molecule compound that we are developing as a treatment for the symptoms associated with carcinoid syndrome; and

LX2931, an orally-delivered small molecule compound that we are developing as a treatment for rheumatoid arthritis and other autoimmune diseases.

We have initiated a Phase 1 clinical trial of LX1033, an orally-delivered small molecule compound that we are developing as a treatment for irritable bowel syndrome and other gastrointestinal disorders, and we have 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.

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 have enabled us to generate 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.

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."

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.

THE OFFERING

The following summary contains basic information about this offering. The summary is not intended to be complete. You should read the full text and more specific details contained elsewhere in this prospectus.

Issuer	Lexicon Pharmaceuticals, Inc.
Common stock offered to public	shares ⁽¹⁾
Common stock to be outstanding after this offering	shares ⁽²⁾
Use of proceeds	The net proceeds of this offering are estimated to be approximately \$ million after the deduction of underwriting discounts and commissions and estimated offering expenses payable by Lexicon based on an assumed public offering price of \$1.46 per share, which is the reported last sales price of our common stock on May 25, 2011. We currently intend to use the net proceeds for research and development. We may also use a portion of the net proceeds to acquire or invest in complementary products and technologies or for general corporate purposes. See “Use of Proceeds.”
Nasdaq Global Select Market symbol	LXRX
Risk Factors	See “Risk Factors” beginning on page 6 and the other information included in, or incorporated by reference into, this prospectus for a discussion of certain factors you should carefully consider before deciding to invest in shares of our common stock.

Except as otherwise indicated, all information in this prospectus assumes no exercise of the underwriters' over-allotment option in this offering.

To the extent that the underwriters exercise their over-allotment option, we will offer Invus, L.P. and Invus C.V., or Invus, the right to purchase a number of additional shares of our common stock sufficient to permit Invus to maintain its percentage ownership of our outstanding common stock after giving effect to the underwriters' exercise of their over-allotment option, which could be up to additional shares of our common stock if the underwriters exercise their over-allotment option in full.

(1)

Includes _____ shares offered directly by us to Invus at the price to the public set forth on the cover page of this prospectus pursuant to Invus' right to purchase up to the number of shares that is sufficient to maintain its pro rata ownership of our common stock.

(2) Based on 337,659,869 shares of our common stock outstanding as of April 30, 2011 and excludes:

21,500,146 shares of common stock issuable upon the exercise of outstanding stock options at a weighted average exercise price per share of \$3.02;

2,552,200 shares of common stock issuable upon vesting of outstanding restricted stock units (phantom stock); and

6,974,389 shares of common stock available for future grant or issuance under our stock incentive plans.

SUMMARY FINANCIAL DATA

The statement of operations data for each of the three years in the period ended December 31, 2010 has been derived from our financial statements that have been audited by Ernst & Young LLP, independent registered public accounting firm. The statements of operations data for the three months ended March 31, 2011 and 2010, and the balance sheet data as of March 31, 2011, are unaudited but include, in the opinion of management, all adjustments, consisting of only normal recurring adjustments, necessary for a fair presentation of such data. Our historical results for any prior or interim periods are not necessarily indicative of results to be expected for any future period.

The data presented below has been prepared in accordance with accounting principles generally accepted in the United States and should be read in conjunction with our financial statements and related notes incorporated by reference in this prospectus.

	Year Ended December 31,			Three Months Ended March 31,	
	2008	2009	2010	2010	2011
	(unaudited)				
	(in thousands, except per share data)				
Statements of Operations Data:					
Revenues	\$32,321	\$10,700	\$4,908	\$1,641	\$596
Operating expenses:					
Research and development	107,232	81,238	78,520	21,088	23,921
Increase in fair value of Symphony Icon, Inc. purchase liability	—	—	2,710	—	1,058
General and administrative	21,624	19,418	19,396	5,519	4,753
Total operating expenses	128,856	100,656	100,626	26,607	29,732
Loss from operations	(96,535)	(89,956)	(95,718)	(24,966)	(29,136)
Interest and other income (expense), net	(349)	(3,463)	(6,083)	(1,104)	(493)
Consolidated net loss before taxes	(96,884)	(93,419)	(101,801)	(26,070)	(29,629)
Income tax benefit	—	102	26	—	—
Consolidated net loss	(96,884)	(93,317)	(101,775)	(26,070)	(29,629)
Less: net loss attributable to noncontrolling interest in Symphony Icon, Inc.	20,024	10,537	—	—	—
Net loss attributable to Lexicon Pharmaceuticals, Inc.	\$(76,860)	\$(82,780)	\$(101,775)	\$(26,070)	\$(29,629)
Net loss attributable to Lexicon Pharmaceuticals, Inc. per common share, basic and diluted	\$(0.56)	\$(0.57)	\$(0.34)	\$(0.13)	\$(0.09)
Shares used in computing net loss attributable to Lexicon Pharmaceuticals, Inc. per common share, basic and diluted share, basic and diluted	136,797	145,465	302,844	197,239	337,527

As of March 31, 2011
Actual As

	Adjusted (2)
	(unaudited)
	(in thousands)
Balance Sheet Data:	
Cash, cash equivalents, and short-term investments ⁽¹⁾	\$188,910 \$
Working capital ⁽¹⁾	178,709
Total assets	343,408
Deferred revenue, net of current portion	14,212
Long-term debt, net of current portion	27,044
Other long-term liabilities	49,610
Accumulated deficit	(703,035)
Lexicon Pharmaceuticals, Inc. stockholders' equity	219,317

(1) Includes restricted investments of \$430 as of March 31, 2011.

Reflects the net proceeds from the sale of shares of common stock in this offering at an assumed public offering price of \$1.46 per share, which is the reported last sale price of our common stock on May 25, 2011, after deducting underwriting discounts and commissions and estimated offering expenses.

RISK FACTORS

You should carefully consider the risk factors and all other information contained in this prospectus and incorporated herein by reference before purchasing shares of our common stock. Investing in our common stock involves a high degree of risk.

For a discussion of these risks, please see:

• Our most recent annual report on Form 10-K, and

• Our other filings with the SEC that are incorporated by reference into this prospectus.

For more information about our SEC filings, please see “Where You Can Find More Information” and “Documents Incorporated By Reference” on page 19 of this prospectus. See also “Special Note Regarding Forward-Looking Statements” on page 10 of this prospectus.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of 900 million shares of common stock, \$0.001 par value, and five million shares of preferred stock, \$0.01 par value. As of April 30, 2011, there were 337,659,869 shares of our common stock issued and outstanding, 217,658 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 restated certificate of incorporation, as amended, 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 restated certificate of incorporation, as amended, restated bylaws and the Delaware General Corporation Law. For information on how to obtain copies of our restated certificate of incorporation, as amended, and restated bylaws, see “Where You Can Find More Information” on page 19 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 common stock have no preemptive rights and no right to convert their common stock into any other securities. 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 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 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;

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- 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, L.P. and Its Affiliates

In June 2007, we entered into a securities purchase agreement with Invus, L.P., under which Invus, L.P. made an initial investment of approximately \$205.5 million to purchase 50,824,986 shares of our common stock in August 2007. Under the securities purchase agreement, as amended and supplemented, and after accounting for the \$181.5 million in net proceeds from our public offering and concurrent private placement of common stock in March 2010, Invus, L.P. and its affiliate Invus C.V., which we collectively refer to as Invus, have the right to require us to initiate a pro rata rights offering to our stockholders, which would provide all stockholders with non-transferable rights to acquire shares of our common stock, in an aggregate amount of up to approximately \$163.0 million. Invus may exercise its right to require us to conduct such a rights offering by giving us notice within a period of one year beginning on February 28, 2011, which will be extended by the number of days during such period that Invus is not permitted under the securities purchase agreement to initiate the rights offering as a result of any “blackout period” in connection with certain public offerings of our common stock. If Invus elects to exercise its right to require us to initiate a rights offering, Invus would be required to purchase its pro rata portion of the offering.

Under the securities purchase agreement, until the later of the completion of the rights offering or the expiration of the period during which Invus may require us to initiate the rights offering, we have agreed not to issue any of our common stock for a per share price of less than \$4.50 without the prior written consent of Invus, except pursuant to an employee or director stock option, incentive compensation or similar plan or to persons involved in the pharmaceutical industry in connection with simultaneous strategic transactions involving such persons in the ordinary course. In addition, if we notify Invus of a proposed public offering for an offering above \$4.50 per share during the period in which Invus may require us to initiate the rights offering, Invus will have a period of 10 business days in which to exercise its right to require us to conduct the rights offering, in which case we would be required to forego the proposed public offering and proceed with the rights offering.

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 the greater of three members or 30% (or the percentage

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of all the outstanding shares of our common stock owned by Invus and its affiliates, if less than 30%) of all members of our board of directors, rounded up to the nearest whole number of directors, and pursuant to which Invus has designated Philippe J. Amouyal, Raymond Debbane and Christopher J. Sobecki. Mr. Debbane is president and chief executive officer of The Invus Group, LLC, an affiliate of Invus, and Mr. Amouyal and Mr. Sobecki are each managing directors of The Invus Group, LLC.

In the event that the number of shares of our common stock owned by Invus and its affiliates ever exceeds 50% of the total number of shares of our common stock then outstanding (not counting for such purpose any shares acquired by Invus from third parties in excess of 40% (or, if higher, its then pro rata amount) of the total number of outstanding shares of common stock, as permitted by the standstill provisions of the stockholders' agreement), from and after that time, Invus will have the right to designate a number of directors equal to the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates, rounded up to the nearest whole number of directors. The directors appointed by Invus have proportionate representation on the compensation committee and corporate governance committee of our board of directors.

Invus' rights with respect to the designation of members of our board of directors and its 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 will also have the right to terminate these provisions at any time following the date on which the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates exceeds 50% (not counting for such purpose any shares acquired by Invus and its affiliates from third parties in excess of 40% (or, if higher, its then pro rata amount) of the total number of outstanding shares of our common stock, as permitted by the standstill provisions of the stockholders' agreement).

Preemptive Rights. Invus has preemptive rights under the stockholders' agreement to participate in future equity issuances by us (including any qualified offering), subject to certain exceptions, so as to maintain its then-current percentage ownership of our capital stock. Subject to certain limitations, Invus will be required to exercise its preemptive rights in advance with respect to certain marketed offerings, in which case it will be obligated to buy its pro rata share of the number of shares being offered in such marketed offering, including any over-allotment (or such lesser amount specified in its exercise of such rights), so long as the sale of the shares were priced within a range within 10% above or below the market price on the date we notified Invus of the offering and we met certain other conditions.

The provisions of the stockholders' agreement relating to preemptive rights will terminate on the earlier to occur of August 28, 2017 and the date on which the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates falls below 10%.

Standstill Provisions. Invus is subject to standstill provisions restricting its ability to purchase or otherwise acquire additional shares of common stock from third parties to an amount that would result in its ownership of our common stock not exceeding 49% of the total number of shares outstanding. These standstill provisions will not apply to the acquisitions of securities by way of stock splits, stock dividends, reclassifications, recapitalizations, or other distributions by us, acquisitions contemplated by the securities purchase agreement and the stockholders' agreement, including in the rights offering and upon Invus' exercise of preemptive rights under the stockholders' agreement.

Except for acquisitions pursuant to the provisions described above, and subject to certain exceptions, Invus has agreed that it will not, and will cause its affiliates not to, without the approval of our unaffiliated board, directly or indirectly: solicit proxies to vote any of our voting securities or any voting securities of our subsidiaries;

submit to our board of directors a written proposal for any merger, recapitalization, reorganization, business combination or other extraordinary transaction involving an acquisition of us or any of our subsidiaries or any of our or our subsidiaries' securities or assets by Invus and its affiliates;

enter into discussions, negotiations, arrangements or understandings with any third party with respect to any of the foregoing; or

request us or any of our representatives, directly or indirectly, to amend or waive any of these standstill provisions.

The standstill provisions of the stockholders' agreement will terminate on the earliest to occur of (a) August 28, 2017, (b) the date on which the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates falls below 10%, (c) the date on which the percentage of all of the outstanding shares of our common stock

owned by Invus and its affiliates exceeds 50% (not counting for such purpose any shares acquired by Invus from third parties in excess of 40% (or, if higher, its then pro rata amount) of the total number of outstanding shares of common stock, as permitted by the standstill provisions of the stockholders' agreement), (d) the date on which any third party makes a public proposal to acquire (by purchase, exchange, merger or otherwise) assets or business constituting 50% or more of our revenues, net income or assets or

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50% of any class of our equity securities or our board of directors recommends or approves, or proposes to recommend or approve, any such transaction or (e) the date on which any third party acquires beneficial ownership (by purchase, exchange, merger or otherwise) of assets or business constituting 20% or more of our revenues, net income or assets or 20% of any class of our equity securities or our board of directors recommends or approves, or proposes to recommend or approve, any such transaction.

Sales to Third Parties. Subject to certain exceptions, Invus has agreed that neither it nor its affiliates will sell any shares of common stock to third parties that are not affiliated with Invus if, to Invus' knowledge, such transfer would result in any such third party (or any person or group including such third party) owning more than 14.9% of the total number of outstanding shares of our common stock.

The provisions of the stockholders' agreement relating to sales to third parties will terminate on the earliest to occur of (a) August 28, 2017, (b) the date on which the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates falls below 10%, and (c) the date on which the percentage of all the outstanding shares of our common stock owned by Invus and its affiliates exceeds 50% (not counting for such purpose any shares acquired by Invus and its affiliates from third parties in excess of 40% (or, if higher, its then pro rata amount) of the total number of outstanding shares of our common stock, as permitted by the standstill provisions of the stockholders' agreement).

Voting of Shares. In any election of persons to serve on our board of directors, Invus will be obligated to vote all of the shares of common stock held by it and its affiliates in favor of the directors nominated by our board of directors, as long as we have complied with our obligation with respect to the designation of members of our board of directors described above and the individuals designated by Invus for election to our board of directors have been nominated, and, if applicable, are serving on our board of directors. With respect to all other matters submitted to a vote of the holders of our common stock, Invus will be obligated to vote any shares that it acquired from third parties in excess of 40% (or, if higher, its then pro rata amount) of the total number of outstanding shares of common stock, as permitted by the standstill provisions of the stockholders' agreement, in the same proportion as all the votes cast by other holders of our common stock, unless Invus and we (acting with the approval of the unaffiliated board) agree otherwise. Invus may vote all other shares of our common stock held by it in its sole discretion.

The provisions of the stockholders' agreement relating to voting will terminate on the earliest to occur of (a) August 28, 2017, (b) the date on which the percentage of all the outstanding shares of our common stock held by Invus and its affiliates falls below 10%, (c) the date on which the percentage of all outstanding shares of our common stock owned by Invus and its affiliates exceeds 50% (not counting for such purpose any shares acquired by Invus from third parties in excess of 40% (or, if higher, its then pro rata amount) of the total number of outstanding shares of our common stock, as permitted by the provisions of the stockholders' agreement), and (d) the termination of the standstill provisions in accordance with the stockholders' agreement.

Minority Protections. Invus is entitled to certain minority protections, including consent rights over (a) the creation or issuance of any new class or series of shares of our capital stock (or securities convertible into or exercisable for shares of our capital stock) having rights, preferences or privileges senior to or on parity with our common stock, (b) any amendment to our certificate of incorporation or bylaws, or amendment to the certificate of incorporation or bylaws of any of our subsidiaries, in a manner adversely affecting Invus' rights under the securities purchase agreement and the related agreements, (c) the repurchase, retirement, redemption or other acquisition of our or our subsidiaries' capital stock (or securities convertible into or exercisable for shares of our or our subsidiaries' capital stock), (d) any increase in the size of our board of directors to more than 12 members and (e) the adoption or proposed adoption of any stockholders' rights plan, "poison pill" or other similar plan or agreement, unless Invus is exempt from the provisions of such plan or agreement.

The provisions of the stockholders' agreement relating to minority protections will terminate on the earlier to occur of August 28, 2017 and the date on which Invus and its affiliates hold less than 15% of the total number of outstanding shares of our common stock.

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

pursuant to this prospectus.

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

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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 restated certificate of incorporation, as amended, requires that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and may not be effected by a consent in writing. Additionally, our restated certificate of incorporation, as amended:

• 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 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 restated certificate of incorporation, as amended. 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 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 BNY Mellon Shareowner Services.

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 within the meaning of Section 27A of the Securities Act and 21E of the Exchange Act. We have attempted to identify forward-looking statements by terminology including “anticipate,” “believe,” “can,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “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 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 other sections of the documents incorporated by reference into this prospectus. 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.

MARKET PRICE OF OUR COMMON STOCK AND RELATED STOCKHOLDER MATTERS

Our common stock is quoted on The Nasdaq Global Select Market under the symbol "LXRX." The following table sets forth, for the periods indicated, the high and low sales prices for our common stock as reported on The Nasdaq Global Select Market, and previously on The Nasdaq Global Market.

	High	Low
2009		
First Quarter	\$1.75	\$0.81
Second Quarter	\$1.63	\$0.94
Third Quarter	\$3.78	\$1.11
Fourth Quarter	\$2.13	\$1.30
2010		
First Quarter	\$2.87	\$1.20
Second Quarter	\$1.69	\$1.19
Third Quarter	\$1.63	\$1.17
Fourth Quarter	\$1.91	\$1.22
2011		
First Quarter	\$2.30	\$1.44
Second Quarter (through May 25, 2011)	\$1.87	\$1.33

As of April 30, 2011, there were approximately 224 holders of record of our common stock.

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.

OUR EXECUTIVE OFFICERS

Our executive officers and their ages and positions are listed below.

Name	Age	Position with the Company
Arthur T. Sands, M.D., Ph.D.	49	President and Chief Executive Officer and Director
Alan J. Main, Ph.D.	57	Executive Vice President of Pharmaceutical Research
Jeffrey L. Wade, J.D.	46	Executive Vice President, Corporate Development and Chief Financial Officer
Brian P. Zambrowicz, Ph.D.	49	Executive Vice President and Chief Scientific Officer
Pablo Lapuerta, M.D.	47	Senior Vice President, Clinical Development and Chief Medical Officer
James F. Tessmer	51	Vice President, Finance and Accounting

Arthur T. Sands, M.D., Ph.D. co-founded our company and has been our president and chief executive officer and a director since September 1995. At Lexicon, Dr. Sands pioneered the development of large-scale gene knockout technology for use in drug discovery. Before founding our company, Dr. Sands served as an American Cancer Society postdoctoral fellow in the Department of Human and Molecular Genetics at Baylor College of Medicine. Dr. Sands received his B.A. in economics and political science from Yale University and his M.D. and Ph.D. from Baylor College of Medicine.

Alan J. Main, Ph.D. has been our executive vice president of pharmaceutical research since February 2007 and served as our senior vice president, Lexicon Pharmaceuticals from July 2001 until February 2007. Dr. Main was president and chief executive officer of Coelacanth Corporation, a leader in using proprietary chemistry technologies to rapidly discover new chemical entities for drug development, from January 2000 until our acquisition of Coelacanth in July 2001. Dr. Main was formerly senior vice president, U.S. Research at Novartis Pharmaceuticals Corporation, where he worked for 20 years before joining Coelacanth. Dr. Main holds a B.S. from the University of Aberdeen, Scotland and a Ph.D. in organic chemistry from the University of Liverpool, England and completed postdoctoral studies at the Woodward Research Institute.

Jeffrey L. Wade, J.D. has been our executive vice president, corporate development and chief financial officer since May 2010. Mr. Wade served as our executive vice president and general counsel from February 2000 until May 2010 and was our senior vice president and chief financial officer from January 1999 to February 2000. From 1988 through December 1998, Mr. Wade was a corporate securities and finance attorney with the law firm of Andrews & Kurth L.L.P., for the last two years as a partner, where he represented companies in the biotechnology, information technology and energy industries. Mr. Wade is a member of the boards of directors of the Texas Healthcare and Bioscience Institute and the Texas Life Science Center for Innovation and Commercialization. He received his B.A. and J.D. from the University of Texas.

Brian P. Zambrowicz, Ph.D. co-founded our company and has been our executive vice president and chief scientific officer since February 2007. Dr. Zambrowicz served as our executive vice president of research from August 2002 until February 2007, senior vice president of genomics from February 2000 to August 2002, vice president of research from January 1998 to February 2000 and senior scientist from April 1996 to January 1998. From 1993 to April 1996, Dr. Zambrowicz served as a National Institutes of Health postdoctoral fellow at the Fred Hutchinson Cancer Center in Seattle, Washington, where he studied gene trapping and gene targeting technology. Dr. Zambrowicz received his B.S. in biochemistry from the University of Wisconsin. He received his Ph.D. from the University of Washington, where he studied tissue-specific gene regulation using transgenic mice.

Pablo Lapuerta, M.D. has been our senior vice president, clinical development and chief medical officer since March 2011. From 2009 through 2010, Dr. Lapuerta served as vice president at Bristol-Myers Squibb Company with responsibility for global development of an Alzheimer's disease drug candidate. From 2007 through 2009, Dr. Lapuerta was senior vice president, clinical strategy and chief medical officer of Cogentus Pharmaceuticals, Inc. and prior to that served in a variety of clinical development leadership roles at Bristol-Myers Squibb, where he worked for 11 years before joining Cogentus. He holds a B.A. in biology from Harvard College and an M.D. from Harvard Medical School.

James F. Tessmer has been our vice president, finance and accounting since November 2007 and previously served as our senior director of finance from February 2004 to November 2007 and director of finance from April 2001 to February 2004. From January 1997 to April 2001, Mr. Tessmer was assistant controller for Mariner Health Network, Inc. and prior to that served in a variety of financial and accounting management positions for HWC Distribution Corp. and American General Corporation. Mr. Tessmer is a certified public accountant and received his B.B.A. from the University of Wisconsin - Milwaukee and his M.B.A. from the University of Houston.

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SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table presents information regarding the beneficial ownership of our common stock as of April 30, 2011 by:

each of the individuals listed in “Executive and Director Compensation - Summary Compensation Table for 2010” in the proxy statement for our 2011 annual meeting of stockholders;

each of our directors;

each person, or group of affiliated persons, who is known by us to own beneficially five percent or more of our common stock; and

all current directors and executive officers as a group.

Beneficial ownership is determined in accordance with the rules of the Securities and Exchange Commission computing the number of shares beneficially owned by a person and the percentage ownership of that person. Shares of common stock underlying options held by that person that are currently exercisable or exercisable within 60 days of April 30, 2011 are considered outstanding. These shares, however, are not considered outstanding when computing the percentage ownership of each other person.

Except as indicated in the footnotes to this table and pursuant to state community property laws, each stockholder named in the table has sole voting and investment power for the shares shown as beneficially owned by them.

Percentage of ownership is based on 337,659,869 shares of common stock outstanding on April 30, 2011. Unless otherwise indicated in the footnotes, the address of each of the individuals named below is: c/o Lexicon Pharmaceuticals, Inc., 8800 Technology Forest Place, The Woodlands, Texas 77381.

	Beneficial Ownership		
	Number of Shares Beneficially Owned	Shares Issuable Pursuant to Options Exercisable within 60 Days of April 30, 2011	Percentage Ownership
Invus, L.P., Invus Public Equities, L.P., Invus C.V. and related parties ⁽¹⁾	165,110,497		48.9%
FMR LLC and related parties ⁽²⁾	40,017,988		11.9%
Arthur T. Sands, M.D., Ph.D. ⁽³⁾	1,663,226	2,511,460	1.2%
Jeffrey L. Wade, J.D.	47,973	1,016,588	*
Alan J. Main, Ph.D.	44,973	1,098,664	*
Brian P. Zambrowicz, Ph.D.	158,851	1,373,130	*
Steven A. Tragash		74,491	*
Ajay Bansal			*
James F. Tessmer	23,469	230,514	*
Philip M. Brown, M.D., J.D. ⁽⁴⁾	24,306		*
Samuel L. Barker, Ph.D.	66,000	141,333	*
Philippe J. Amouyal		54,166	*
Raymond Debbane ⁽⁵⁾	165,110,497	54,166	48.9%
Robert J. Lefkowitz, M.D.		79,666	*
Alan S. Nies, M.D.	5,000	100,166	*
Frank P. Palantoni		81,666	*
Christopher J. Sobecki	1,000	54,166	*
Judith L. Swain, M.D.		54,166	*
All current directors and executive officers as a group ⁽³⁾⁽⁵⁾ (14 persons)	167,120,989	6,849,851	50.5%

* Represents beneficial ownership of less than 1 percent.

(1) Based upon a Schedule 13D/A filed with the SEC on March 19, 2010, reflecting the beneficial ownership of our common stock by Invus, L.P., Invus Public Equities, L.P., Invus C.V. and related parties. Invus, L.P. and related parties may be deemed to have sole investment and voting power with respect to 131,436,780 of such shares and shared voting power with respect to 3,891,108 of such shares. Invus Public Equities, L.P. and related parties may be deemed to have sole investment and shared voting power with respect to 3,891,108 of such shares. Invus C.V. and related parties may be deemed to have sole investment and voting power with respect to 29,782,609 of such shares. All of such shares are subject to certain voting restrictions pursuant to our stockholders' agreement with Invus, L.P. and Invus C.V. described under the heading "Description of Capital Stock - Arrangements with Invus, L.P. and

its Affiliates.” The address for Invus, L.P. and Invus Public Equities, L.P. is Clarendon House, 2 Church Street, Hamilton HM II, Bermuda. The address for Invus C.V. is Marten Meesweg 25, Rotterdam 3068 AV, Netherlands. The address for all related parties is c/o The Invus Group, LLC, 750 Lexington Avenue, 30th Floor, New York, New York 10022.

(2) Based upon a Schedule 13G filed with the SEC on February 14, 2011, reflecting the beneficial ownership of our common stock by FMR LLC and related parties. FMR LLC and Edward C. Johnson 3d each have sole investment power with respect to the shares. The address for FMR LLC and all related parties is 82 Devonshire Street, Boston, Massachusetts 02109.

(3) The number of shares beneficially owned by Dr. Sands includes 60,000 shares held in the name of minor children and 817,500 shares owned by Sands Associates LP. The general partners of Sands Associates LP are ATS Associates, L.L.C., owned by Dr. Sands, and MES Associates, L.L.C., owned by Dr. Sands' wife.

(4) Based upon certain representations made to us by Dr. Brown.

(5) Based upon a Schedule 13D/A filed with the SEC on March 19, 2010, reflecting the beneficial ownership by Mr. Debbane of the shares of our common stock beneficially owned by Invus, L.P., Invus Public Equities, L.P., Invus C.V. and related parties. Mr. Debbane disclaims beneficial ownership of these shares. The address for Mr. Debbane is c/o The Invus Group, LLC, 750 Lexington Avenue, 30th Floor, New York, New York 10022.

CAPITALIZATION

The following table presents our unaudited capitalization and other data as of March 31, 2011 on an actual basis and as adjusted to give effect to the sale by us of shares of common stock in this offering, based on an assumed public offering price of \$1.46 per share and after deducting estimated underwriting discounts and commissions and estimated offering expenses. To the extent the actual public offering price per share in this offering is higher or lower than \$1.46, the number of shares we elect to sell is greater or less than the number herein indicated or the underwriters exercise their over-allotment option, our net proceeds will be adjusted in proportion to such changes. See “Use of Proceeds” on page 19. You should read the following table in conjunction with the consolidated financial statements and the related notes incorporated by reference into this prospectus.

	As of March 31, 2011	
	Actual	As Adjusted
	(in thousands, except share data)	
Cash, cash equivalents, restricted cash and investments	\$ 188,910	\$
Long-term debt, net of current portion	\$ 27,044	\$
Stockholders' equity:		
Preferred stock, \$0.01 par value; 5,000,000 shares authorized, no shares issued and outstanding	—	—
Common stock, \$0.001 par value; 900,000,000 shares authorized; 337,874,527 shares issued, actual; shares issued, as adjusted	338	
Additional paid-in capital	922,319	
Accumulated deficit	(703,035) ()
Accumulated other comprehensive gain	40	
Treasury stock, at cost, 217,658 shares	(345) ()
Total Lexicon Pharmaceuticals, Inc. stockholders' equity	219,317	
Total capitalization	\$ 246,361	\$

The table above excludes 21,463,244 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2011 at a weighted average exercise price of \$3.04 per share, 2,557,200 shares of common stock issuable upon vesting of restricted stock units outstanding as of March 31, 2011 and 7,010,162 shares of common stock available for future grant or issuance under our stock incentive plans as of March 31, 2011.

DILUTION

As of March 31, 2011, our net tangible book value was approximately \$121.2 million, or approximately \$0.36 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 337,874,527 shares of our common stock outstanding as of March 31, 2011. After giving effect to our sale of shares of common stock in this offering, based on the assumed public offering price of \$1.46 per share and after deducting estimated underwriting discounts and commissions and estimated offering expenses, based on the assumed public offering price, the net tangible book value as of March 31, 2011 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 assumed 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, 2011	\$0.36
Increase in net tangible book value per share attributable to new investors	
Net tangible book value per share as of March 31, 2011 after giving effect to this offering	
Dilution in net tangible book value per share to new investors	\$

As of March 31, 2011, there were outstanding options to purchase a total of 21,463,244 shares of common stock at a weighted average exercise price of \$3.04 per share and 2,557,200 shares of common stock issuable upon vesting of restricted stock units. To the extent that any of these stock options are exercised and restricted stock units vest, there may be further dilution to new public investors.

UNDERWRITING

Under the terms and subject to the conditions contained in an underwriting agreement which we will enter into with the underwriters named below, for whom _____ is acting as representative, such underwriters have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares of common stock indicated below:

Name	Number of Shares
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Total

The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement will provide that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus are subject to the approval of various legal matters by their counsel and to other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' over-allotment option described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the public offering price listed on the cover page of this prospectus and part to certain dealers at a price that represents a concession not in excess of \$ _____ a share under the public offering price. No underwriter may allow and no dealer may re-allow, any concessions to other underwriters or to certain dealers. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives. We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase up to an aggregate of _____ additional shares of common stock at the public offering price set forth on the cover page of this prospectus, less underwriting discounts and commissions. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with the offering of the shares of common stock offered by this prospectus. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

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

	No Exercise	Full Exercise
Per share	\$	\$
Total	\$	\$

The underwriters have informed us that they do not intend sales to discretionary accounts to exceed five percent of the total number of shares of common stock offered by them.

We, our directors and executive officers and Invus will enter into customary lock-up agreements with the underwriters pursuant to which, without the prior written consent of _____ on behalf of the underwriters, during the period ending _____ days after the date of this prospectus, not to:

offer, pledge, 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 common stock or any securities convertible into or exercisable or exchangeable for common stock; or

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enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise, subject to certain exceptions.

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In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the over-allotment option. The underwriters can close out a covered short sale by exercising the over-allotment option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the over-allotment option. The underwriters may also sell shares in excess of the over-allotment option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. As an additional means of facilitating the offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. The underwriting syndicate may also reclaim selling concessions allowed to an underwriter or a dealer for distributing the common stock in the offering, if the syndicate repurchases previously distributed common stock to cover syndicate short positions or to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. These transactions may be effected on The Nasdaq Global Select Market, in the over-the-counter market or otherwise. The underwriters are not required to engage in these activities, and may end any of these activities at any time.

We and the underwriters will agree to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus in electronic format may be made available on the websites maintained by one or more of the underwriters, and one or more of the underwriters may distribute prospectuses electronically. Other than the prospectus in electronic format, the information on any of these websites and any other information contained on a website maintained by an underwriter or syndicate member is not part of this prospectus. The underwriters may agree to allocate a number of shares to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the underwriters that make Internet distributions on the same basis as other allocations.

USE OF PROCEEDS

We intend to use the net proceeds from the sale of common stock offered pursuant to this prospectus for research and development and 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 product development efforts. Accordingly, our management will retain broad discretion in the allocation of the net proceeds from the sale(s) of the offered shares of common stock.

LEGAL MATTERS

The validity of the issuance of the shares of common stock 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, 2010, as set forth in their report, which is 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 report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file 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 the SEC's Public Reference Room at 100 F Street, NE, Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for information about the operation of its Public Reference Room 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 <http://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 and does not constitute a part of this prospectus.

This prospectus is part of a registration statement we filed with the SEC relating to the shares of common stock offered hereby. 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 may refer to the registration statement, exhibits and schedules for more information about us and the common stock. The registration statements, exhibits and schedules are available at the SEC's public reference room or through its website.

DOCUMENTS INCORPORATED BY REFERENCE

The SEC allows us to "incorporate by reference" certain 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. We incorporate by reference the documents listed below that we have previously filed with the SEC:

- our annual report on Form 10-K for the year ended December 31, 2010;
- our quarterly report on Form 10-Q for the quarterly period ended March 31, 2011;
- our current reports on Form 8-K dated February 23 and April 28, 2011 and our current report on Form 8 K/A dated July 30, 2010 and filed on March 16, 2011; and
- 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 Securities Exchange Act of 1934, 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

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.

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.

8800 Technology Forest Place

The Woodlands, Texas 77381-1160

Telephone: (281) 863-3000

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 13. Other Expenses of Issuance and Distribution.

The estimated expenses payable by the Registrant in connection with the issuance and distribution of the shares of common stock being registered (other than underwriting discounts and commissions) are as follows:

SEC Registration Fee	\$23,220
Printing Expenses	25,000
Accounting Fees and Expenses	25,000
Legal Fees and Expenses	100,000
Transfer Agent and Registrar Fees	3,000
Miscellaneous Expenses	3,780
Total	\$180,000

Item 14. Indemnification of Directors and Officers.

Section 145 of the Delaware General Corporation Law (“DGCL”) provides that a corporation may indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding whether civil, criminal, administrative or investigative (other than an action by or in the right of the corporation) by reason of the fact that he is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by him in connection with such action, suit or proceeding if he acted in good faith and in a manner he reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe his conduct was unlawful. Section 145 further provides that a corporation similarly may indemnify any such person serving in any such capacity who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor by reason of the fact that he is or was a director, officer, employee or agent of the corporation or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees) actually and reasonably incurred in connection with the defense or settlement of such action or suit if he acted in good faith and in a manner he reasonably believed to be in or not opposed to the best interests of the corporation and except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation unless and only to the extent that the Delaware Court of Chancery or such other court in which such action or suit was brought shall determine upon application that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which the Delaware Court of Chancery or such other court shall deem proper.

Lexicon's restated certificate of incorporation, as amended, and restated bylaws provide that indemnification shall be to the fullest extent permitted by the DGCL for all current or former directors or officers. As permitted by the DGCL, the restated certificate of incorporation provides that directors of Lexicon shall have no personal liability to Lexicon or its stockholders for monetary damages for breach of fiduciary duty as a director, except (1) for any breach of the director's duty of loyalty to Lexicon or its stockholders, (2) for acts or omissions not in good faith or which involve intentional misconduct or knowing violation of law, (3) under Section 174 of the DGCL or (4) for any transaction from which a director derived an improper personal benefit.

Lexicon has entered into indemnification agreements with each of its officers and directors. These agreements, among other things, require Lexicon to indemnify each officer and director for all expenses, including attorneys' fees, liabilities, judgments, fines, penalties, excise taxes and settlement amounts incurred by any such person in any claim, action, suit or proceeding, including any action by or in the right of Lexicon, arising out of the person's services as a

director, officer, employee, agent or fiduciary to Lexicon, any subsidiary of Lexicon or to any other company or enterprise for which the person provides services at Lexicon's request.

At present, there is no pending litigation or proceeding involving a director or officer of Lexicon as to which indemnification is being sought nor is Lexicon aware of any threatened litigation that may result in claims for indemnification by any officer or director.

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Item 15. Recent Sales of Unregistered Securities.

None.

Item 16. Exhibits and Financial Statement Schedules.

(a)List of Exhibits

Exhibit No.	Description
*1.1	— Form of Underwriting Agreement.
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- 10.13 — Non-Employee Directors' Stock Option Plan (filed as Exhibit 10.2 to the Company's Current Report on Form 8-K dated April 23, 2009 and incorporated by reference herein).
- 10.14 — Coelacanth Corporation 1999 Stock Option Plan (filed as Exhibit 99.1 to the Company's Registration Statement on Form S-8 (Registration No. 333-66380) and incorporated by reference herein).
- 10.15 — Form of Stock Option Agreement with Chairman of Board of Directors under the Equity Incentive Plan (filed as Exhibit 10.17 to the Company's Annual Report on Form 10-K for the period ended December 31, 2005 and incorporated by reference herein).
- 10.16 — Form of Stock Option Agreement with Directors under the Non-Employee Directors' Stock Option Plan (filed as Exhibit 10.15 to the Company's Annual Report on Form 10-K for the year ended December 31, 2009 and incorporated by reference herein).
- 10.17 — Form of Stock Option Agreement with Officers under the Equity Incentive Plan (filed as Exhibit 10.16 to the Company's Annual Report on Form 10-K for the year ended December 31, 2009 and incorporated by reference herein).
- 10.18 — Form of Stock Bonus Agreement with Officers under the Equity Incentive Plan (filed as Exhibit 10.2 to the Company's Current Report on Form 8-K dated February 23, 2011 and incorporated by reference herein).
- 10.19 — Form of 2010 Restricted Stock Unit Agreement with Officers under the Equity Incentive Plan (filed as Exhibit 10.2 to the Company's Current Report on Form 8-K dated February 15, 2010 and incorporated by reference herein).
- 10.20 — Form of 2011 Restricted Stock Unit Agreement with Officers under the Equity Incentive Plan (filed as Exhibit 10.3 to the Company's Current Report on Form 8-K dated February 23, 2011 and incorporated by reference herein).
- †10.21 — Collaboration and License Agreement, dated December 17, 2003, with Bristol-Myers Squibb Company (filed as Exhibit 10.15 to the amendment to the Company's Annual Report on Form 10-K/A for the period ended December 31, 2003, as filed on July 16, 2004, and incorporated by reference herein).
- †10.22 — First Amendment, dated May 30, 2006, to Collaboration and License Agreement, dated December 17, 2003, with Bristol-Myers Squibb Company (filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q for the period ended June 30, 2006, and

incorporated by reference herein).

- †10.23 — Collaboration Agreement, dated July 27, 2004, with Takeda Pharmaceutical Company Limited (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the period ended September 30, 2004 and incorporated by reference herein).
- †10.24 — Collaboration and License Agreement, dated February 16, 2010, with N.V. Organon and its affiliates Intervet Inc. and Schering Corporation, acting through its Schering-Plough Research Institute division (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the period ended March 31, 2010 and incorporated by reference herein).
- †10.25 — Second Amended and Restated Collaboration and License Agreement, dated November 30, 2005, with Genentech, Inc. (filed as Exhibit 10.22 to the Company's Annual Report on Form 10-K for the period ended December 31, 2005 and incorporated by reference herein).

10.26	—	Amendment, dated June 8, 2009, to Second Amended and Restated Collaboration and License Agreement, dated November 30, 2005, with Genentech, Inc. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K/A dated June 8, 2009 and incorporated by reference herein).
10.27	—	Economic Development Agreement dated July 15, 2005, with the State of Texas and the Texas A&M University System (filed as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q for the period ended September 30, 2005 and incorporated by reference herein).
10.28	—	Amendment, dated April 30, 2008, to Economic Development Agreement, dated July 15, 2005, with the State of Texas and the Texas A&M University System (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated April 30, 2008 and incorporated by reference herein).
10.29	—	Loan and Security Agreement, dated April 21, 2004, between Lex-Gen Woodlands, L.P. and iStar Financial Inc. (filed as Exhibit 10.18 to the Company's Annual Report on Form 10-K for the period ended December 31, 2004 and incorporated by reference herein).
10.30	—	Lease Agreement, dated May 23, 2002, between Lexicon Pharmaceuticals (New Jersey), Inc. and Townsend Property Trust Limited Partnership (filed as Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q for the period ended June 30, 2002 and incorporated by reference herein).
21.1	—	Subsidiaries (filed as Exhibit 21.1 to the Company's Annual Report on Form 10-K for the period ended December 31, 2010 and incorporated by reference herein).
± 23.1	—	Consent of Independent Registered Public Accounting Firm.
23.2	—	Consent of Vinson & Elkins L.L.P. (contained in Exhibit 5.1).

* To be filed by amendment, as an exhibit to a report filed under the Securities Exchange Act of 1934, as amended, or as otherwise required by regulation of the Securities and Exchange Commission, and incorporated by reference herein.

† Confidential treatment has been requested for a portion of this exhibit. The confidential portions of this exhibit have been omitted and filed separately with the Securities and Exchange Commission.

± Filed herewith.

(b) Financial Statement Schedules

The information required by this Item is hereby incorporated by reference from the financial statements and related notes included in the Registrant's Annual Report on Form 10-K for the period ended December 31, 2010 and Quarterly Report on Form 10-Q for the period ended March 31, 2011.

Item 17. Undertakings.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Act and will be governed by the final adjudication of such issue.

The Registrant hereby undertakes that:

(a) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the Registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

(b) For the purpose of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

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SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the Registrant certifies that it has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of The Woodlands, in the State of Texas, on May 26, 2011.

Lexicon Pharmaceuticals, Inc.

By: *
 Arthur T. Sands, M.D., Ph.D.
 President and Chief Executive Officer

PURSUANT TO THE REQUIREMENTS OF THE SECURITIES ACT OF 1933, AS AMENDED, THIS REGISTRATION STATEMENT HAS BEEN SIGNED BELOW BY THE FOLLOWING PERSONS IN THE CAPACITIES AND ON THE DATES INDICATED BELOW.

Signature	Title	Date
* Arthur T. Sands, M.D., Ph.D.	President, Chief Executive Officer and Director (principal executive officer)	May 26, 2011
* Jeffrey L. Wade	Executive Vice President, Corporate Development and Chief Financial Officer (principal financial officer)	May 26, 2011
* James F. Tessmer	Vice President, Finance and Accounting (principal accounting officer)	May 26, 2011
* Samuel L. Barker, Ph.D.	Chairman of the Board of Directors	May 26, 2011
* Philippe J. Amouyal	Director	May 26, 2011
* Raymond Debbane	Director	May 26, 2011
* Robert J. Lefkowitz, M.D.	Director	May 26, 2011
* Alan S. Nies, M.D.	Director	May 26, 2011
* Frank P. Palantoni	Director	May 26, 2011
* Christopher J. Sobecki	Director	May 26, 2011
* Judith L. Swain, M.D.	Director	May 26, 2011

*By: /s/ Jeffrey L. Wade
 Jeffrey L. Wade
 Pursuant to powers-of-attorney filed
 with the Registration Statement on
 Form S-3 (333-171953) on January 28,
 2011

EXHIBIT INDEX

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