

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)

Delaware

2834

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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8800 Technology Forest Place
The Woodlands, Texas 77381-1160
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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.

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)	Proposed Maximum Aggregate Offering Price (1) (2)	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 Genome5000™ is 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.

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.

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 "LXXR."

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 RIGHTS OFFERING

The following summary contains basic information about this rights offering and is not intended to be complete. For a more detailed description of the terms and conditions of the rights offering, please see the section entitled “The Rights Offering.”

Issuer	Lexicon Pharmaceuticals, Inc.
Total number of shares of common stock available for subscription	shares
Securities offered	We are distributing to you, at no charge, one non-transferable subscription right for every share of our common stock that you own as of 5:00 p.m., New York time, on the record date, either as a holder of record or, in the case of shares held of record by brokers, dealers, custodian banks or other nominees on your behalf, as a beneficial owner of such shares.
Subscription price	[\$•] per share.
Basic subscription privilege	The basic subscription privilege of each subscription right will entitle you to purchase shares of our common stock at a subscription price of [\$•] per share. 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.
Over-subscription privilege	If you purchase all of the shares of common stock available to you pursuant to your basic subscription privilege, you may also choose to subscribe for shares of our common stock that are not purchased by other holders through the exercise of their basic subscription privileges. You may subscribe for shares of our common stock pursuant to your over-subscription privilege, subject to proration of available shares.
Record date	5:00 p.m., New York time, on [•], 2011.
Expiration date	5:00 p.m., New York time, on [•], 2011, unless we and Invus agree to extend the rights offering period.
Transferability of rights	The subscription rights are non-transferable during the course of the subscription period.

No recommendation

Our board of directors makes no recommendation about whether you should exercise any of your subscription rights. You are urged to make an independent investment decision about whether to exercise your subscription rights based on your own assessment of our business and the rights offering.

No revocation

Any exercise of subscription rights is irrevocable, even if Invus does not exercise its basic subscription privilege in full because certain customary closing conditions are not satisfied or you later learn information that you consider to be unfavorable to the exercise of your subscription rights. See the section entitled "Description of Capital Stock - Arrangements with Invus, L.P. and Its Affiliates." You should not exercise your subscription rights unless you are certain that you wish to purchase additional shares of common stock at the subscription price of \$[•] per share.

Material United States federal income tax consequences	<p>For United States federal income tax purposes, you will not recognize income or loss upon receipt or exercise of subscription rights. You should consult your own tax advisor as to your particular tax consequences resulting from the rights offering. For a detailed discussion, see the section entitled “Material United States Federal Income Tax Consequences.”</p>
Purchase commitment	<p>Invus is required to exercise its basic subscription privilege in full and purchase at least share of our common stock in the rights offering, subject to certain customary closing conditions. See the section entitled “Description of Capital Stock - Arrangements with Invus, L.P. and Its Affiliates.”</p>
Extension, cancellation, and amendment	<p>With Invus' consent, we have the option to extend the rights offering and the period for exercising your subscription rights, although we do not presently intend to do so. With Invus' consent, we may also cancel the rights offering at any time for any reason. If the rights offering is cancelled, all subscription payments received by the subscription agent will be returned promptly, without interest or penalty. With Invus' consent, we also reserve the right to amend or modify the terms of the rights offering.</p>
Procedure for exercising rights	<p>To exercise your subscription rights, you should take the following steps:</p> <p>If you are a registered holder of shares of our common stock, you may exercise your subscription rights by delivering payment and a properly completed subscription rights certificate and election form to the subscription agent before 5:00 p.m., New York time, on [•], 2011. You may make delivery by mail or commercial carrier. If regular mail is used for this purpose, we recommend using registered mail, properly insured, with return receipt requested.</p> <p>If you are a beneficial owner of shares that are registered in the name of a broker, dealer, custodian bank or other nominee, we will instruct your broker, dealer, custodian bank or other nominee to provide you with materials relating to the rights offering. You may exercise your subscription rights by following the instructions contained in the rights offering materials in order to direct your broker, dealer, custodian bank or other nominee to exercise your subscription rights on your behalf and deliver all documents and payments to the subscription agent before 5:00 p.m., New York time, on [•], 2011. You should promptly contact</p>

your broker, dealer, custodian bank or other nominee if you believe you are entitled to participate in the rights offering, but have not received any rights offering materials.

Subscription agent

BNY Mellon Shareowner Services.

Information agent

BNY Mellon Shareowner Services.

Use of proceeds

Assuming the full subscription, the net proceeds of the rights offering are estimated to be approximately \$[•] million after the deduction of estimated expenses. We currently intend to use the net proceeds for research and development and general corporate purposes. We may also use a portion of the net proceeds to acquire or invest in complementary businesses, products and technologies. See the section entitled “Use of Proceeds.”

Risk Factors	See the section entitled “Risk Factors” 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 exercise your subscription rights and invest in our common stock.
Fees and expenses	We will pay the fees and expenses relating to the rights offering.

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 June 30, 2011 and 2010, and the balance sheet data as of June 30, 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,			Six Months Ended	
	2008	2009	2010	June 30,	2011
				(unaudited)	
	(in thousands, except per share data)				
Statements of Operations Data:					
Revenues	\$32,321	\$10,700	\$4,908	\$2,874	\$1,151
Operating expenses:					
Research and development	107,232	81,238	78,520	41,327	44,066
Increase in fair value of Symphony Icon, Inc. purchase liability	—	—	2,710	—	2,862
General and administrative	21,624	19,418	19,396	10,587	9,285
Total operating expenses	128,856	100,656	100,626	51,914	56,213
Loss from operations	(96,535)	(89,956)	(95,718)	(49,040)	(55,062)
Interest and other income (expense), net	(349)	(3,463)	(6,083)	(2,223)	(1,205)
Consolidated net loss before taxes	(96,884)	(93,419)	(101,801)	(51,263)	(56,267)
Income tax benefit	—	102	26	—	—
Consolidated net loss	(96,884)	(93,317)	(101,775)	(51,263)	(56,267)
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)	\$(51,263)	\$(56,267)
Net loss attributable to Lexicon Pharmaceuticals, Inc. per common share, basic and diluted	\$(0.56)	\$(0.57)	\$(0.34)	\$(0.19)	\$(0.17)
Shares used in computing net loss attributable to Lexicon Pharmaceuticals, Inc. per	136,797	145,465	302,844	267,709	337,598

common share, basic and
dilutedshare, basic and diluted

	As of June 30, 2011			As
	Actual			Adjusted
	(unaudited)			(2)
	(in thousands)			
Balance Sheet Data:				
Cash, cash equivalents, and short-term investments ⁽¹⁾	\$ 164,814	164,814	164,814	\$
Working capital ⁽¹⁾	155,967	155,967	155,967	
Total assets	315,916	315,916	315,916	
Deferred revenue, net of current portion	14,212	14,212	14,212	
Long-term debt, net of current portion	24,188	24,188	24,188	
Other long-term liabilities	51,357	51,357	51,357	
Accumulated deficit			(729,673)	
Lexicon Pharmaceuticals, Inc. stockholders' equity	194,188	194,188	194,188	

(1) Includes restricted investments of \$430 as of June 30, 2011.

(2) Reflects the net proceeds from the sale of shares of common stock in this rights offering at a price of \$[] per share.

QUESTIONS AND ANSWERS RELATING TO THE RIGHTS OFFERING

The following are examples of what we anticipate will be common questions about the rights offering, but do not contain all of the information that may be important to you and may not address all of the questions you may have about the rights offering. For a more detailed description of the terms and conditions of the rights offering, please see the section entitled “The Rights Offering.”

Exercising the subscription rights and investing in our common stock involves risks. The following questions and answers do 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.

What is the rights offering?

We are distributing to holders of our common stock as of 5:00 p.m., New York time, on [•], 2011 or the “record date,” at no charge, non-transferable subscription rights to purchase shares of our common stock. You will receive one subscription right for every share of our common stock you owned as of 5:00 p.m., New York time, on the record date. The subscription rights will be evidenced by a subscription rights certificate and election form.

What is a subscription right?

Each subscription right gives our stockholders the opportunity to purchase _____ shares of our common stock for \$[•] per share and carries with it both a basic subscription privilege and an over-subscription privilege, as described below.

How many shares may I purchase if I exercise my subscription rights?

Each subscription right entitles you to purchase _____ shares of our common stock for \$[•] per share. For example, if you owned 100 shares of our common stock on the record date, you would be granted 100 subscription rights and you would have the right to purchase _____ shares of our common stock (_____ rounded down to the nearest whole number) for an aggregate purchase price of \$[•]. You may exercise any number of your subscription rights, or you may choose not to exercise any subscription rights. 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.

What is the basic subscription privilege?

Each subscription right evidences a basic subscription privilege to purchase _____ shares of our common stock at the subscription price of \$[•] per share.

What is the over-subscription privilege?

Each subscription right also evidences an over-subscription privilege to purchase additional shares of our common stock at the same subscription price per share as under the basic subscription privilege under certain circumstances. You must have subscribed for the maximum number of shares permitted by your basic subscription privilege in order to exercise your over-subscription privilege. You must indicate on your subscription rights certificate (or beneficial owner election form, in the case of shareholders that hold through a broker, dealer, custodian bank or other nominee) by the expiration date whether and to what extent you elect to exercise your over-subscription privilege.

If sufficient shares of common stock are available, we will seek to honor your over-subscription request in full.

However, if over-subscription requests exceed the aggregate number of shares of common stock available for sale pursuant to the over-subscription privilege, we will allocate the available shares of common stock pro rata among each eligible person properly exercising the over-subscription privilege in proportion to the number of shares of common stock each such person owned as of the record date. If any person subscribes for a fewer number of shares pursuant to the over-subscription privilege than otherwise allocated to such person pursuant to this pro rata allocation, then such person will be allocated only that number of shares for which the person over-subscribed, and the remaining shares of common stock will be allocated among all other persons exercising in full their over-subscription privilege on a pro rata basis in proportion to the number of shares allocated to such persons pursuant to their over-subscription privileges. The proration process will be repeated until all shares of common stock have been allocated or all over-subscription requests have been satisfied, whichever occurs earlier.

Am I required to exercise all of the rights I receive in the rights offering?

No. You may exercise any number of your subscription rights, or you may choose not to exercise any subscription rights. However, if you choose not to exercise your basic subscription privilege in full, the relative percentage of our shares of common stock that you own will decrease, and your voting and other rights will be diluted. In addition, if you do not exercise your basic subscription privilege in full, you will not be entitled to participate in the over-subscription privilege.

Why are we conducting the rights offering?

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." 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, Invus has the right to require us to initiate a pro rata rights offering to our stockholders providing 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 exercised its right to require us to conduct such a rights offering on [•], 2011.

Will Invus be exercising its subscription rights?

Pursuant to the terms of the securities purchase agreement, as amended and supplemented, Invus is required to exercise its basic subscription privilege in full and purchase at least _____ shares of our common stock in the rights offering, subject to certain customary closing conditions.

Has our board of directors made a recommendation to our stockholders regarding the exercise of rights under the rights offering?

No. Our board of directors is making no recommendation regarding the exercise of your subscription rights. Stockholders who exercise their subscription rights risk loss on their investment. We cannot assure you that the market price of our common stock will be above the subscription price or that anyone purchasing shares at the subscription price will be able to sell those shares in the future at the same price or a higher price. You are urged to make your decision based on your own assessment of our business and financial condition, the terms of the rights offering and the information contained or incorporated by reference in this prospectus.

How was the subscription price of \$[•] per share determined?

Pursuant to the terms of the securities purchase agreement, as amended and supplemented, Invus has the right to designate a subscription price in a range between \$4.50 per share and the average of the volume weighted average trading prices of our common stock on the Nasdaq Global Select Market for the ten full trading days prior to such designation. Invus designated a subscription price of \$[•] per share on [•], 2011.

How soon must I exercise my rights?

The subscription rights will expire and will have no value if not exercised prior to [•], 2011, at 5:00 p.m., New York time, unless we and Invus agree to extend the rights offering period. If you are a registered holder of our common stock, the subscription agent must receive your completed and signed subscription rights certificate and payment prior to the expiration of the rights offering. If you hold your shares in street name through a broker, dealer, custodian bank or other nominee, your broker, dealer, custodian bank or other nominee may establish a deadline prior to [•], 2011, at 5:00 p.m. for the submission of instructions as to the exercise of your subscription rights.

May I transfer my rights?

No. Should you choose not to exercise your subscription rights, you may not sell, give away, or otherwise transfer your subscription rights. Subscription rights will, however, be transferable by operation of law (for example, upon the death of the recipient). Upon expiration of the rights offering, all unexercised rights will automatically expire.

Are we requiring a minimum subscription to complete the rights offering?

There is no minimum subscription requirement in the rights offering. However, with Invus' consent, we may cancel the rights offering at any time for any reason, including if we believe that there is insufficient participation by our stockholders. If

the rights offering is cancelled, all subscription payments received by the subscription agent will be returned promptly, without interest or penalty.

Can the rights offering be canceled, terminated, amended or extended?

Yes. With Invus' consent, we have the option to extend the rights offering and the period for exercising your subscription rights, although we do not presently intend to do so. With Invus' consent, we may also cancel or terminate the rights offering at any time for any reason. If the rights offering is cancelled or terminated, all subscription payments received by the subscription agent will be returned promptly, without interest or penalty. With Invus' consent, we also reserve the right to amend or modify the terms of the rights offering for any reason.

When will I receive the subscription rights certificate or other rights offering materials?

Promptly after the date of this prospectus, the subscription agent will send a subscription rights certificate and election form to each registered holder of our common stock as of the close of business on the record date, based on our stockholder registry maintained by the transfer agent for our common stock. If you hold your shares of common stock in street name through a broker, dealer, custodian bank or other nominee, you will not receive a subscription rights certificate and election form. Instead, we will instruct your broker, dealer, custodian bank or other nominee to provide you with materials relating to the rights offering which you may use to direct your broker, dealer, custodian bank or other nominee to exercise your subscription rights on your behalf. You should promptly contact your broker, dealer, custodian bank or other nominee if you believe you are entitled to participate in the rights offering, but have not received any rights offering materials.

What will happen if I choose not to exercise my subscription rights?

If you do not exercise any subscription rights, the number of our shares of common stock you own will not change. Due to the fact that Invus is required to fully exercise its basic subscription right and shares may be purchased pursuant to the rights offering by other stockholders, your percentage ownership of our common stock will be diluted following completion of the rights offering, unless you fully exercise your basic subscription rights. See the section entitled "Risk Factors - Your interest in us may be diluted as a result of this offering."

How do I exercise my subscription rights?

If you are a registered holder of shares of our common stock, you may exercise your subscription rights by delivering payment and a properly completed subscription rights certificate and election form to the subscription agent before 5:00 p.m., New York time, on [•], 2011. If you wish to exercise your over-subscription privilege, you should indicate on your completed subscription rights certificate and election form the number of shares you wish to purchase pursuant to your over-subscription privilege and include payment related to such shares. Please follow the payment and delivery instructions accompanying the subscription rights certificate and election form.

If you send a payment that is insufficient to purchase the number of shares you requested, or if the number of shares requested is not specified, your subscription rights will be exercised to the fullest extent possible based on the amount of the payment received, subject to the availability of shares under the over-subscription privilege and the elimination of fractional shares. Any excess subscription payments received by the subscription agent will be returned promptly, without interest or penalty, following the expiration of the rights offering.

You may make delivery by mail or commercial carrier. If regular mail is used for this purpose, we recommend using registered mail, properly insured, with return receipt requested. We also urge you to allow sufficient time for delivery so that payment and the completed subscription rights certificate are received by the subscription agent by no later than the expiration date. Please do not make any delivery relating to the rights offering directly to Lexicon.

How do I exercise my subscription rights if my shares are held in the name of my broker, dealer, custodian bank or other nominee?

If you are a beneficial owner of shares that are registered in the name of a broker, dealer, custodian bank or other nominee, you will not receive a subscription rights certificate and election form, and your broker, dealer, custodian bank or other nominee must exercise your subscription rights on your behalf. We will instruct your broker, dealer, custodian bank or other nominee to provide you with materials relating to the rights offering. You may exercise your subscription rights by following the instructions contained in the rights offering materials in order to direct your broker, dealer, custodian bank or other nominee to exercise your subscription rights on your behalf. Your broker, dealer, custodian bank or other nominee may establish a

deadline prior to [•], 2011, at 5:00 p.m. for the submission of instructions as to the exercise of your subscription rights. You should promptly contact your broker, dealer, custodian bank or other nominee if you believe you are entitled to participate in the rights offering, but have not received any rights offering materials.

When will I receive the shares of common stock I purchase in the rights offering?

If you are a registered holder of shares of our common stock, we will mail you a stock certificate evidencing the shares purchased in the rights offering as soon as practicable after the completion of the rights offering. One stock certificate will be generated for each subscription rights certificate processed.

If you are a beneficial owner of shares that are registered in the name of a broker, dealer, custodian bank or other nominee, you will not receive stock certificates for the shares purchased in the rights offering. Rather, your broker, dealer, custodian bank or other nominee will be credited on your behalf for the shares of common stock you purchase in the rights offering as soon as practicable after the completion of the rights offering.

After I exercise my subscription rights, can I change my mind and cancel my purchase?

No. Once you exercise and send in your subscription rights certificate and payment, you may not revoke the exercise of your subscription rights, even if Invus does not exercise its basic subscription privilege in full because the Invus Closing Conditions are not satisfied or you later learn information that you consider to be unfavorable to the exercise of your subscription rights. See the section entitled "Description of Capital Stock-Arrangements with Invus, L.P. and Its Affiliates." You should not exercise your subscription rights unless you are certain that you wish to purchase additional shares of our common stock at a subscription price of \$[•] per share.

How many shares of common stock will be outstanding after the rights offering?

As of [•], 2011, _____ shares of our common stock were outstanding. The number of shares of our common stock that will be outstanding after the rights offering will depend on the number of shares that are purchased in the rights offering. If we sell all of the shares offered in the rights offering and issue no additional shares of our common stock pursuant to the exercise of stock options or vesting of restricted stock units, then _____ shares of common stock will be outstanding after the closing of the rights offering.

Are there risks in exercising my subscription rights?

Yes. The exercise of your subscription rights involves risks. Exercising your subscription rights involves the purchase of additional shares of common stock and should be considered as carefully as you would consider any other equity investment. Please see the section entitled "Risk Factors."

If the rights offering is not completed, will my subscription payment be refunded to me?

Yes. The subscription agent will hold all funds it receives in a segregated bank account until completion of the rights offering. If the rights offering is not completed, all subscription payments received by the subscription agent will be returned promptly, without interest or penalty. If you own shares in street name through a broker, dealer, custodian bank or other nominee, the subscription agent will return payments through the record holder of your shares, which may result in a longer period for you to receive payment.

How do I exercise my rights if I live outside the United States?

This prospectus and the subscription rights certificates will not be delivered to stockholders whose addresses are outside the United States or who have an Army Post Office or foreign post office address. If you are a foreign stockholder or a stockholder with an Army Post Office or foreign post office address, you must notify the subscription agent prior to 11:00 a.m., New York time, at least three business days prior to the expiration of the rights offering of your exercise of such rights and, if your address is outside the United States, provide satisfactory evidence that the exercise of such rights does not violate the laws of your jurisdiction.

What fees or charges apply if I purchase the shares of common stock?

We are not charging any fee or sales commission to issue subscription rights to you or to issue shares to you if you exercise your subscription rights. If you exercise your subscription rights through your broker, dealer, custodian bank or other nominee, you are responsible for paying any fees charged by your broker, dealer, custodian bank or other nominee.

What are the material United States federal income tax consequences of exercising my subscription rights?

For United States federal income tax purposes, you will not recognize income or loss upon receipt or exercise of subscription rights. However, you should consult your tax advisor as to your particular tax consequences resulting from the rights offering. Please see the section entitled "Material United States Federal Income Tax Consequences."

To whom should I send my forms and payment?

If you are a registered holder of our common stock, you should send your payment and properly completed subscription rights certificate and election form by hand delivery, first class mail or courier service to:

If Delivering by Mail:

BNY Mellon Shareowner Services
Attn:Corporate Action Department, 27th Floor
P.O. Box 3301
South Hackensack, New Jersey 07606

If Delivering by Hand or Courier:

BNY Mellon Shareowner Services
Attn:Corporate Action Department, 27th Floor
480 Washington Boulevard
Jersey City, New Jersey 07310

Your payment of the subscription price must be made in United States dollars for the full number of shares of our common stock for which you are subscribing by cashier's or certified check drawn upon a United States bank payable to the subscription agent at the address set forth above. You are solely responsible for completing delivery to the subscription agent of your subscription materials.

If your shares are held in the name of a broker, dealer, custodian bank or other nominee, you should send your subscription documents to that record holder and follow the instructions contained in the rights offering materials delivered to you.

Whom should I contact if I have other questions?

If you have any questions about the rights offering or wish to request another copy of a document, please contact BNY Mellon Shareowner Services, our information agent, from within the U.S., Canada or Puerto Rico toll free at (800) 777-3674, or if you are located outside of the U.S., at (201) 680-6579.

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. In particular, you should carefully consider and evaluate the risks and uncertainties described in “Part I - Item 1A. Risk Factors” of our most recent Form 10-K for the year ended December 31, 2010 and in “Part II - Item 1A. Risk Factors” of our Form 10-Q for the quarterly period ended June 30, 2011, in each case as updated by the additional risks and uncertainties set forth in other filings we make with the SEC.

Risks Relating to the Rights Offering

Your interest in us may be diluted as a result of this offering.

Stockholders who do not fully exercise their basic subscription rights should expect that they will, at the completion of this offering, own a smaller proportional interest in us than would otherwise be the case had they fully exercised their rights.

You could be committed to buying shares of common stock above the prevailing market price.

Once you exercise your rights, you may not revoke such exercise even if you later learn information that you consider to be unfavorable to the exercise of your subscription rights. Our shares of common stock are traded on the Nasdaq Global Select Market under the symbol “LXRX.” On [•], 2011, the last trading day before this offering was publicly announced, the closing price of our shares of common stock on the Nasdaq Global Select Market was \$[•] per share. On [•], 2011, the last trading day before the commencement of this offering, the closing price of our shares of common stock was \$[•] per share. We cannot assure you that the market price of our shares of common stock will not decline prior to the expiration of this offering or that, after shares of common stock are issued upon exercise of rights, a subscribing rights holder will be able to sell shares of common stock purchased in this offering at a price greater than or equal to the subscription price.

The subscription price determined for this offering may not be an indication of the value of our common stock.

Pursuant to the terms of our securities purchase agreement with Invus, L.P., as amended and supplemented, Invus has the right to designate a subscription price in a range between \$4.50 per share and the average of the volume weighted average trading prices of our common stock on the Nasdaq Global Select Market for the ten full trading days prior to such designation. Invus designated a subscription price of \$[•] per share on [•], 2011.

The subscription price may not be an indication of the value of our common stock. We cannot assure you that the market price for our common stock during the rights offering will be equal to or above the subscription price or that a subscribing owner of rights will be able to sell the shares of common stock purchased in the rights offering at a price equal to or greater than the subscription price. We urge you to obtain a current quote for our common stock before exercising your subscription rights. After the date of this prospectus, our common stock may trade at prices below the subscription price.

We will have broad discretion in the use of the net proceeds from this offering and may not use them in ways that increase the value of your investment.

We will generally have broad discretion in determining how the net proceeds from this offering will be used. Our management may not use the net proceeds in ways that increase the value of your investment, and you will be relying on the judgment of our management regarding the application of these proceeds. We currently intend to use the net proceeds for research and development and may also use a portion of the net proceeds to acquire or invest in complementary businesses, products and technologies or for general corporate purposes. We have not otherwise allocated the net proceeds from this offering for any specific purposes. Until we use the net proceeds, we plan to invest them, and these investments may not yield a favorable rate of return. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

If we cancel or terminate this offering, neither we nor the subscription agent will have any obligation to you except to return your subscription payments.

We may cancel or terminate this offering only with the consent of Invus. If we cancel or terminate this offering, neither we nor the subscription agent will have any obligation with respect to rights that have been exercised except to return, without interest or deduction, any subscription payments the subscription agent received from you.

If you do not act on a timely basis and follow subscription instructions, your exercise of rights may be rejected. Holders of shares of common stock who desire to purchase shares of our common stock in this offering must act on a timely basis to ensure that all required forms and payments are actually received by the subscription agent prior to 5:00 p.m., New

York time, on the expiration date, unless extended. If you are a beneficial owner of shares of common stock and you wish to exercise your rights, you must act promptly to ensure that your broker, custodian bank or other nominee acts for you and that all required forms and payments are actually received by your broker, custodian bank or other nominee in sufficient time to deliver such forms and payments to the subscription agent to exercise the rights granted in this offering that you beneficially own prior to 5:00 p.m., New York time on the expiration date, unless extended. We will not be responsible if your broker, custodian or nominee fails to ensure that all required forms and payments are actually received by the subscription agent prior to 5:00 p.m., New York time, on the expiration date, unless extended.

If you fail to complete and sign the required subscription forms, send an incorrect payment amount, or otherwise fail to follow the subscription procedures that apply to your exercise in this offering, the subscription agent may, depending on the circumstances, reject your subscription or accept it only to the extent of the payment received.

Neither we nor the subscription agent undertakes to contact you concerning an incomplete or incorrect subscription form or payment, nor are we under any obligation to correct such forms or payment. We have the sole discretion to determine whether a subscription exercise properly follows the subscription procedures.

If you make payment of the subscription price by uncertified check, your check may not clear in sufficient time to enable you to purchase shares in this rights offering.

Any uncertified check used to pay for shares to be issued in this rights offering must clear prior to the expiration date of this rights offering, and the clearing process may require five or more business days. If you choose to exercise your subscription rights, in whole or in part, and to pay for shares by uncertified check and your check has not cleared prior to the expiration date of this rights offering, you will not have satisfied the conditions to exercise your subscription rights and will not receive the shares you wish to purchase.

If the rights offering is not fully subscribed, Invus may increase its ownership.

On the record date for the rights offering, Invus and its affiliates beneficially owned approximately [•] % of our outstanding common stock. As holders of our common stock as of the record date, Invus and its affiliates will have the right to subscribe for and purchase shares of our common stock under the basic subscription right of the rights offering and will have the right to participate in the over-subscription privilege. To the extent that Invus and its affiliates and other holders of our common stock exercise their basic subscription rights and any over-subscription rights, the ownership percentage of Invus and its affiliates of our outstanding common stock may increase or decrease, including to over 50% of our outstanding common stock and, if Invus and its affiliates exercise their basic subscription right in full and are the only holders of rights who exercise the basic subscription right, up to approximately [•] % of our outstanding common stock. In addition, the ownership percentage of Invus and its affiliates may further increase depending on the extent to which Invus and its affiliates exercise their over-subscription rights under such circumstances. Your interests as a holder of common stock may differ materially from the interests of Invus. See “-If as a result of the rights offering Invus' ownership percentage exceeds 50% of our outstanding common stock, certain restrictions on Invus contained in our stockholders' agreement may terminate.”

If as a result of the rights offering Invus' ownership percentage exceeds 50% of our outstanding common stock, certain restrictions on Invus contained in our stockholders' agreement may terminate.

Under the stockholders' agreement we entered into in connection with Invus, L.P.'s \$205.5 million initial investment in our common stock, Invus currently has the right to designate the greater of three members or 30% (or the percentage 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, pursuant to which Invus has designated Raymond Debbane, president and chief executive officer of The Invus Group, LLC, an affiliate of Invus, and Philippe J. Amouyal and Christopher J. Sobecki, each of whom are 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 after June 17, 2007 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 and corporate governance committees of our board of directors.

In addition, 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 acquisitions of securities by way of stock splits, stock dividends, reclassifications, recapitalizations, or other distributions by us or 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 after June 17, 2007 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 50% of any class of our equity securities 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.

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 after June 17, 2007 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).

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 after June 17, 2007 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 after June 17, 2007 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.

If as a result of the rights offering 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 after June 17, 2007 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), the provisions of the stockholders' agreement discussed above may

or will terminate, and Invus may or will have the ability to designate a majority of the members of our board of directors and to control actions to be taken by us, including amendments to our certificate of incorporation and bylaws and the approval of significant corporate transactions, including mergers, sales of substantially all of our assets, distributions of our assets and the incurrence of indebtedness. Your interests as a holder of common stock may differ materially from the interests of Invus.

You will not be able to sell the shares of common stock you buy in the rights offering until you receive your stock certificates or your account is credited with the common stock.

If you purchase shares in the rights offering by submitting a subscription rights certificate and payment, we will mail you a stock certificate as soon as practicable after [•], 2011, or such later date as to which the rights offering may be extended. If your shares are held by a broker, dealer, custodian bank or other nominee and you purchase shares, your account with your nominee will be credited with the shares of our common stock you purchased in the rights offering as soon as practicable after the expiration of the rights offering, or such later date as to which the rights offering may be extended. Until your stock certificates have been delivered or your account is credited, you may not be able to sell your shares even though the common stock issued in the rights offering will be listed for trading on the Nasdaq. The stock price may decline between the time you decide to sell your shares and the time you are actually able to sell your shares.

For more information about our SEC filings, please see the sections entitled “Where You Can Find More Information” and “Documents Incorporated By Reference.” See also the section entitled “Special Note Regarding Forward-Looking Statements.”

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 [•], 2011, there were _____ shares of our common stock issued and outstanding, _____ 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 the section entitled "Where You Can Find More Information."

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;
- 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 (the “securities purchase agreement”), 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 has the right to require us to initiate a pro rata rights offering to our stockholders providing 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 exercised its right to require us to conduct such a rights offering on [•], 2011. Invus is required to exercise its basic subscription privilege in full and purchase at least shares of our common stock in the rights offering, subject to certain customary closing conditions, including (1) the expiration or termination of any applicable waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, (2) the accuracy (subject to materiality and material adverse effect qualifications) of our representations and warranties set forth in the securities purchase agreement, as of the closing of the rights offering (except that those representations and warranties that address matters only as of a particular date need only remain true and correct, subject to any materiality qualifiers, as of such date), (3) our performance or compliance in all material respects with the agreements and covenants to be performed by us under the securities purchase agreement and related ancillary agreements on or before the closing of the rights offering, (4) the delivery of a certificate signed by our president certifying as to the satisfaction of the closing conditions set forth in clauses (2) and (3) above, (5) the delivery of an opinion of counsel reasonably satisfactory to Invus and covering certain matters specified in the securities purchase agreement and (6) the delivery of certificates of good standing for us and our material subsidiaries (collectively, the “Invus Closing Conditions”).

Under the securities purchase agreement, until the completion of 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.

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 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 after June 17, 2007 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 after June 17, 2007 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 overallotment (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 after June 17, 2007 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 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.

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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 after June 17, 2007 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 after June 17, 2007 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 after June 17, 2007 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 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	\$1.87	\$1.33
Third Quarter (through August 10, 2011)	\$1.85	\$1.30

As of [•], 2011, there were approximately [•] holders of record of our common stock.

On [•], 2011, the last trading day before this offering was publicly announced, the closing price of our shares of common stock on the Nasdaq Global Select Market was \$[•] per share. On [•], 2011, the last trading day before the commencement of this offering, the closing price of our shares of common stock was \$[•] per share.

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.	48	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.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table presents information regarding the beneficial ownership of our common stock as of [•], 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 [•], 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 shares of common stock outstanding on [•], 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		Percentage Ownership
	Number of Shares Beneficially Owned	Shares Issuable Pursuant to Options Exercisable within 60 Days of [•], 2011	
Invus, L.P., Invus Public Equities, L.P., Invus C.V. and related parties ⁽¹⁾	165,110,497		%
FMR LLC and related parties ⁽²⁾	40,017,988		%
Arthur T. Sands, M.D., Ph.D. ⁽³⁾	1,663,226		%
Jeffrey L. Wade, J.D.	47,973		*
Alan J. Main, Ph.D.	44,973		*
Brian P. Zambrowicz, Ph.D.	158,851		*
Steven A. Tragash			*
Ajay Bansal			*
James F. Tessmer	23,469		*
Philip M. Brown, M.D., J.D. ⁽⁴⁾	24,306		*
Samuel L. Barker, Ph.D.	66,000		*
Philippe J. Amouyal			*
Raymond Debbane ⁽⁵⁾	165,110,497		%
Robert J. Lefkowitz, M.D.			*
Alan S. Nies, M.D.	5,000		*
Frank P. Palantoni			*
Christopher J. Sobecki	1,000		*
Judith L. Swain, M.D.			*
All current directors and executive officers as a group ⁽³⁾⁽⁵⁾ (14 persons)	167,120,989		%

* 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.

THE RIGHTS OFFERING

The Subscription Rights

We are distributing, at no charge, to the record holders of our common stock as of [•], 2011, or the record date, non-transferable subscription rights to purchase additional shares of our common stock at a subscription price of \$[•] per share. Each record holder will receive one subscription right for each share of common stock owned by such holder as of 5:00 p.m., New York time on the record date, entitling such holder to both a basic subscription privilege and an over-subscription privilege.

The subscription rights will entitle the holders of our common stock to purchase an aggregate of _____ shares of our common stock. We intend to keep the rights offering open until [•], 2011, unless our board of directors, with Invus' consent, extends such time period or otherwise terminates the rights offering.

Basic Subscription Privilege

Each basic subscription privilege entitles you to purchase _____ shares of our common stock at the subscription price of \$[•] per share, upon delivery of the required documents and payment of the subscription price prior to the expiration of the rights offering. You may exercise all or a portion of your basic subscription privilege; however, if you exercise less than your full basic subscription privilege, you will not be entitled to purchase shares pursuant to your over-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, with the total subscription payment being adjusted accordingly. Any excess subscription payments received by the subscription agent will be returned promptly, without interest or penalty.

Over-Subscription Privilege

You must have subscribed for the maximum number of shares permitted by your basic subscription privilege in order to exercise your over-subscription privilege. You must indicate on your subscription rights certificate and election form (or beneficial owner election form, in the case of shareholders that hold through a broker, dealer, custodian bank or other nominee) by the expiration date whether and to what extent you elect to exercise your over-subscription privilege. If sufficient shares of common stock are available, we will seek to honor the over-subscription requests in full. However, if over-subscription requests exceed the aggregate number of shares of common stock available for sale pursuant to the over-subscription privilege, we will allocate the available shares of common stock pro rata among each eligible person properly exercising the over-subscription privilege in proportion to the number of shares of common stock each such person owned as of the record date. If any eligible person subscribes for a fewer number of shares pursuant to the over-subscription privilege than otherwise allocated to such person pursuant to this pro rata allocation, then such person will be allocated only that number of shares for which the person over-subscribed, and the remaining shares of common stock will be allocated among all other persons exercising in full their over-subscription privilege on a pro rata basis in proportion to the number of shares allocated to such persons pursuant to their over-subscription privileges. The proration process will be repeated until all shares of common stock have been allocated or all over-subscription requests have been satisfied, whichever occurs earlier.

If you wish to exercise your over-subscription rights, you should indicate the number of additional shares that you would like to purchase in the space provided on your subscription rights certificate and election form or other rights offering materials provided by your broker, dealer, custodian bank or other nominee. When you send in your subscription rights certificate and election form to the subscription agent or instructions to your broker, dealer, custodian bank or other nominee, you must also send payment for the full subscription price of the additional shares that you have requested to purchase (in addition to the payment due for shares purchased through your basic subscription rights). As soon as practicable after the expiration date, the subscription agent will determine the number of shares of common stock that you may purchase pursuant to the over-subscription privilege. If you request and pay for more shares than are allocated to you, the subscription agent will refund the overpayment promptly, without interest or penalty.

Method of Exercising Subscription Rights

The exercise of subscription rights is irrevocable and may not be cancelled or modified, even if Invus does not exercise its basic subscription privilege in full because the Invus Closing Conditions are not satisfied or you later learn

information that you consider to be unfavorable to the exercise of your subscription rights. You may exercise your subscription rights as follows:

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Subscription by Registered Holders

If you are a registered holder of shares of our common stock, the number of rights you may exercise pursuant to the basic subscription privilege will be indicated on the subscription rights certificate and election form delivered to you. You may exercise your subscription rights by properly completing and executing the subscription rights certificate and election form and forwarding it, together with your full subscription payment, to the subscription agent at the address set forth below in this section under the heading “Subscription Agent,” prior to the expiration of the rights offering.

Subscription by DTC Participants

We expect that the exercise of your subscription rights may be made through the facilities of the Depository Trust Company, or DTC. If your subscription rights are held of record through DTC, you may exercise your subscription rights by instructing DTC, or having your broker instruct DTC, to transfer your subscription rights from your account to the account of the subscription agent, together with certification as to the aggregate number of subscription rights you are exercising and the number of shares of our common stock you are subscribing for under your basic subscription privilege and your over-subscription privilege, if any, and your full subscription payment.

Subscription by Beneficial Owners

If you are a beneficial owner of shares that are registered in the name of a broker, dealer, custodian bank or other nominee, you will not receive a subscription rights certificate and election form. Instead, one subscription right will be issued to the nominee record holder on your behalf for each share of our common stock that you own at the record date. We will instruct your broker, dealer, custodian bank or other nominee to provide you with materials relating to the rights offering. You may exercise your subscription rights by following the instructions contained in the rights offering materials in order to direct your broker, dealer, custodian bank or other nominee to exercise your subscription rights on your behalf. Your broker, dealer, custodian bank or other nominee may establish a deadline prior to the expiration date of the rights offering for the submission of instructions as to the exercise of your subscription rights. You should promptly contact your broker, dealer, custodian bank or other nominee if you believe you are entitled to participate in the rights offering, but have not received any rights offering materials.

Method of Payment

Payments must be made in full in United States dollars for the full number of shares of our common stock for which you are subscribing by cashier's or certified check drawn upon a United States bank payable to the subscription agent at the address set forth below in this section under the heading “Subscription Agent.”

Personal checks are not accepted. Payment received after the expiration of the rights offering may not be honored, and the subscription agent will return your payment to you promptly, without interest or penalty.

Registered holders should read and follow the delivery and payment instructions accompanying the subscription rights certificate and election form. **DO NOT SEND RIGHTS OFFERING MATERIALS OR PAYMENTS DIRECTLY TO LEXICON PHARMACEUTICALS, INC.** We will not consider your subscription received until the subscription agent has received delivery of a properly completed and duly executed subscription rights certificate and election form and payment of the full subscription amount. The risk of delivery of all documents and payments is borne by you or your nominee, not by the subscription agent or us.

The method of delivery of subscription rights certificates and election form and payment of the subscription amount to the subscription agent will be at the risk of the holders of subscription rights. If sent by mail, we recommend that you send subscription materials and payments by overnight courier or by registered mail, properly insured, with return receipt requested, and that a sufficient number of days be allowed to ensure delivery to the subscription agent and clearance of payment prior to the expiration of the rights offering.

Unless a subscription rights certificate and election form provides that the shares of our common stock are to be delivered to the record holder of such rights or such certificate is submitted for the account of a bank or a broker, signatures on such subscription rights certificate and election form must be guaranteed by an “eligible guarantor institution” (as such term is defined in Rule 17Ad-15 of the Securities Exchange Act of 1934, as amended) that is a participant in the Securities Transfer Agents Medallion Program, the New York Stock Exchange Program Medallion Signature Program or the Stock Exchange Medallion Program, subject to any standards and procedures adopted by the subscription agent.

Missing or Incomplete Subscription Information

If you send a payment that is insufficient to purchase the number of shares you requested, or if the number of shares requested is not specified, your subscription rights will be exercised to the fullest extent possible based on the amount of the payment received, subject to the availability of shares under the over-subscription privilege and the elimination of fractional shares. Any excess subscription payments received by the subscription agent will be returned promptly, without interest or penalty, following the expiration of the rights offering.

Subscription Price

Pursuant to the terms of our securities purchase agreement with Invus, L.P., as amended and supplemented, Invus has the right to designate a subscription price in a range between \$4.50 per share and the average of the volume weighted average trading prices of our common stock on the Nasdaq Global Select Market for the ten full trading days prior to such designation. Invus designated a subscription price of \$[•] per share on [•], 2011.

We cannot assure you that the market price for our common stock during the rights offering will be equal to or above the subscription price or that a subscribing owner of rights will be able to sell the shares of common stock purchased in the rights offering at a price equal to or greater than the subscription price. We urge you to obtain a current quote for our common stock before exercising your subscription rights.

No Transfer of Subscription Rights

The subscription rights are not transferable. Should you choose not to exercise your subscription rights, you may not sell, give away, or otherwise transfer your subscription rights. Subscription rights will, however, be transferable by operation of law (for example, upon the death of the recipient). Upon expiration of the rights offering, all unexercised rights will automatically expire.

No Revocation of Exercise of Subscription Rights

Once you submit your completed subscription rights certificate and election form to exercise any subscription rights, you will not be permitted to revoke or change the exercise or request a refund of monies paid. All exercises of subscription rights are irrevocable, even if Invus does not exercise its basic subscription privilege in full because the Invus Closing Conditions are not satisfied or you later learn information that you consider to be unfavorable to the exercise of your subscription rights. You should not exercise your subscription rights unless you are certain that you wish to purchase additional shares of our common stock at the subscription price.

Expiration Date and Amendments

The subscription period during which you may exercise your subscription rights expires at 5:00 p.m., New York time, on [•], 2011, which is the expiration of the rights offering. If you do not exercise your subscription rights prior to that time, your subscription rights will expire and will no longer be exercisable. We will not be required to issue shares of common stock to you if the subscription agent receives your subscription rights certificate and election form and subscription payment after that time, regardless of when the subscription rights certificate and election form and subscription payment were sent by you. We have the option to extend the rights offering and the period for exercising your subscription rights, with Invus' consent, although we do not presently intend to do so. With Invus' consent, we may extend the expiration of the rights offering by giving oral or written notice to the subscription agent prior to the expiration of the rights offering. If we elect to extend the expiration of the rights offering, we will issue a press release announcing such extension no later than 9:00 a.m., New York time, on the next business day after the most recently announced expiration of the rights offering. With Invus' consent, we also reserve the right to amend or modify the terms of the rights offering for any reason.

Conditions, Withdrawal and Termination

With Invus' consent, we reserve the right to withdraw the rights offering prior to the completion of the rights offering for any reason. We may terminate the rights offering, in whole or in part, if at any time before completion of the rights offering there is any judgment, order, decree, injunction, statute, law or regulation entered, enacted, amended or held to be applicable to the rights offering that in the sole judgment of our board of directors and Invus would or might make the rights offering or its completion, whether in whole or in part, illegal or otherwise restrict or prohibit completion of the rights offering. Pursuant to the terms of our securities purchase agreement with Invus, L.P., the closing of the rights offering is subject to certain customary conditions. We or Invus, as applicable, may waive any of these conditions and choose to proceed with the rights offering even if one or more of the conditions do not occur. If

we cancel or terminate the rights offering, in whole or in part, all affected subscription rights will expire without value, and all excess subscription payments received by the subscription agent will be

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returned promptly, without interest or penalty. If we cancel or terminate the rights offering, we will issue a press release notifying stockholders of the cancellation or termination, and all subscription payments received by the subscription agent will be returned promptly, without interest or penalty.

Delivery of Shares of Common Stock Acquired in the Rights Offering

If you are a registered holder of shares of our common stock, we will mail you a stock certificate evidencing the shares purchased in the rights offering as soon as practicable after the completion of the rights offering. One stock certificate will be generated for each subscription rights certificate processed.

If you are a beneficial owner of shares that are registered in the name of a broker, dealer, custodian bank or other nominee, you will not receive stock certificates for the shares purchased in the rights offering. Rather, your broker, dealer, custodian bank or other nominee will be credited on your behalf for the shares of common stock you purchase in the rights offering as soon as practicable after the completion of the rights offering.

Reasons for the Rights Offering

We are conducting the rights offering at the election of Invus. 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, Invus has the right to require us to initiate a pro rata rights offering to our stockholders providing 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 exercised its right to require us to conduct such a rights offering on [•], 2011.

Participation by Invus in the Rights Offering

Pursuant to the terms of the securities purchase agreement, as amended and supplemented, Invus is required to exercise its basic subscription privilege in full, subject to certain customary closing conditions, and purchase at least _____ shares of our common stock in the rights offering, representing approximately [•]% of the total number of shares available in the rights offering.

Subscription Agent

The subscription agent for this offering is BNY Mellon Shareowner Services. The address to which completed subscription rights certificates and subscription payments should be mailed or delivered is:

If Delivering by Mail:

BNY Mellon Shareowner Services
Attn:Corporate Action Department, 27th Floor
P.O. Box 3301
South Hackensack, New Jersey 07606

If Delivering by Hand or Courier:

BNY Mellon Shareowner Services
Attn:Corporate Action Department, 27th Floor
480 Washington Boulevard
Jersey City, New Jersey 07310

You are solely responsible for completing delivery to the subscription agent of your subscription materials. The subscription materials are to be received by the subscription agent on or prior to 5:00 p.m., New York time, on [•], 2011. We urge you to allow sufficient time for delivery of your subscription materials to the subscription agent. If you deliver subscription materials in a manner different from those described in this prospectus, we may not honor the exercise of your subscription rights.

Fees and Expenses

We are not charging any fee or sales commission to issue subscription rights to you or to issue shares to you if you exercise your subscription rights. If you exercise your subscription rights through your broker, dealer, custodian bank or other nominee, you are responsible for paying any fees charged by your broker, dealer, custodian bank or other nominee.

Fractional Shares

We will not issue fractional shares. Fractional shares of common stock resulting from the exercise of subscription rights will be eliminated by rounding down to the nearest whole share.

Medallion Guarantee May Be Required

Your signature on each subscription rights certificate and election form must be guaranteed by an eligible institution, such as a member firm of a registered national securities exchange or a member of the Financial Industry Regulatory Authority, Inc.,

or a commercial bank or trust company having an office or correspondent in the United States, subject to standards and procedures adopted by the subscription agent, unless:

• your subscription rights certificate provides that shares are to be delivered to you as record holder of those subscription rights; or

• you are an eligible institution.

You can obtain a signature guarantee from a financial institution - such as a commercial bank, savings bank, credit union or broker dealer - that participates in one of the Medallion signature guarantee programs. The three Medallion signature guarantee programs are the following:

• Securities Transfer Agents Medallion Program (STAMP) whose participants include more than 7,000 U.S. and Canadian financial institutions.

• Stock Exchanges Medallion Program (SEMP) whose participants include the regional stock exchange member firms and clearing and trust companies.

• New York Stock Exchange Medallion Signature Program (MSP) whose participants include NYSE member firms.

If a financial institution is not a member of a recognized Medallion signature guarantee program, it would not be able to provide signature guarantees. Also, if you are not a customer of a participating financial institution, it is likely the financial institution will not guarantee your signature. Therefore, the best source of a Medallion Guarantee would be a bank, savings and loan association, brokerage firm, or credit union with which you do business. The participating financial institution will use a Medallion imprint or stamp to guarantee the signature, indicating that the financial institution is a member of a Medallion signature guarantee program and is an acceptable signature guarantor.

Notice to Nominees

If you are a broker, dealer, custodian bank or other nominee holder that holds shares of our common stock for the account of others on the record date, you should notify the beneficial owners of the shares for whom you are the nominee of the rights offering as soon as possible to learn their intentions with respect to exercising their subscription rights. You should obtain instructions from the beneficial owner, as set forth in the instructions we have provided to you for your distribution to beneficial owners. If the beneficial owner so instructs, you should submit information and payment for shares. We expect that the exercise of subscription rights on behalf of beneficial owners may be made through the facilities of DTC. You may exercise individual or aggregate beneficial owner subscription rights by instructing DTC to transfer subscription rights from your account to the account of the subscription agent, together with certification as to the aggregate number of subscription rights exercised and the number of common shares subscribed for under the basic subscription privilege and the over-subscription privilege, if any, and your full subscription payment.

Validity of Subscriptions

We will resolve all questions regarding the validity and form of the exercise of your subscription rights, including time of receipt and eligibility to participate in the rights offering. Our determination will be final and binding. Once made, subscriptions and directions are irrevocable, and we will not accept any alternative, conditional or contingent subscriptions or directions. We reserve the absolute right to reject any subscriptions or directions not properly submitted or the acceptance of which would be unlawful. You must resolve any irregularities in connection with your subscriptions before the subscription period expires, unless waived by us in our sole discretion. Neither we nor the subscription agent shall be under any duty to notify you or your representative of defects in your subscriptions. A subscription will be considered accepted, subject to our right to withdraw or terminate the rights offering, only when a properly completed and duly executed subscription rights certificate and election form and any other required documents and the full subscription payment have been received by the subscription agent. Our interpretations of the terms and conditions of the rights offering will be final and binding.

Escrow Arrangements; Return of Funds

The subscription agent will hold funds received in payment for shares of our common stock in a segregated account pending completion of the rights offering. The subscription agent will hold this money in escrow until the rights offering is completed or is withdrawn and canceled. If the rights offering is canceled for any reason, all subscription payments received by the subscription agent will be returned promptly, without interest or penalty.

Stockholder Rights

You will have no rights as a holder of our shares of common stock you purchase in the rights offering, if any, until certificates representing our shares of common stock are issued to you or until your account with your broker, dealer, custodian bank or other nominee is credited with shares of common stock purchased in the rights offering. You will have no right to revoke your subscriptions once made in accordance with the procedures set forth in this prospectus.

Foreign Stockholders

This prospectus and the subscription rights certificates and election form will not be delivered to stockholders whose addresses are outside the United States or who have an Army Post Office or foreign post office address. Rather, the subscription agent will hold subscription rights certificates and election form for their account. To exercise their subscription rights, foreign stockholders or stockholders with an Army Post Office or foreign post office address must notify the subscription agent prior to 11:00 a.m., New York time, at least three business days prior to the expiration of the rights offering of their exercise of such rights, and, with respect to holders whose addresses are outside the United States, provide evidence satisfactory to us, such as a legal opinion from local counsel, that the exercise of such rights does not violate the laws of the jurisdiction of such stockholder.

Material United States Federal Income Tax Consequences

For United States federal income tax purposes, you will not recognize income or loss upon receipt or exercise of subscription rights. However, you should consult your tax advisor as to your particular tax consequences resulting from the rights offering. Please see the section entitled "Material United States Federal Income Tax Consequences."

MATERIAL UNITED STATES FEDERAL INCOME TAX CONSEQUENCES

The following discussion summarizes the material United States federal income tax consequences of the rights offering to a holder of our common stock that is a United States holder (as defined below). This summary is based upon provisions of the Internal Revenue Code of 1986, as amended, which we refer to as the “Code,” applicable United States Treasury regulations promulgated thereunder, published rulings and pronouncements of the United States Internal Revenue Service, which we refer to as the “IRS,” and judicial decisions in effect on the date hereof, all of which are subject to change (possibly with retroactive effect) and to differing interpretations. No assurance can be given that the IRS would not assert, or that a court would not sustain, a position contrary to any of the tax consequences described below.

This summary is for general information only and does not purport to discuss all aspects of United States federal income taxation that may be important to a particular holder in light of its particular circumstances or to holders that may be subject to special tax rules, including, but not limited to, partnerships or other pass-through entities, banks and other financial institutions, tax-exempt entities, employee stock ownership plans, certain former citizens or residents of the United States, insurance companies, regulated investment companies, real estate investment trusts, dealers in securities or currencies, brokers, traders in securities that have elected to use the mark-to-market method of accounting, persons holding subscription rights or shares of common stock as part of an integrated transaction, including a “straddle,” “hedge,” “constructive sale” or “conversion transaction,” persons whose functional currency for tax purposes is not the United States dollar, and persons subject to the alternative minimum tax provisions of the Code. This summary applies to you only if you are a United States holder and receive your subscription rights in the rights offering, and you hold your subscription rights or shares of common stock issued to you upon exercise of the subscription rights or, if applicable, the over-subscription privilege, as capital assets for tax purposes. This summary does not apply to you if you are not a United States holder.

We have not sought, and will not seek, a ruling from the IRS regarding the United States federal income tax consequences of the rights offering or the related share issuances. The following summary does not address the tax consequences of the rights offering or the related share issuance under foreign, state, or local tax laws.

You are a “United States holder” if you are a beneficial owner of subscription rights or common stock and you are:

- An individual who is a citizen or resident of the United States for United States federal income tax purposes;
- A corporation (or other business entity treated as a corporation for United States federal income tax purposes) created or organized in or under the laws of the United States, or any political subdivision thereof, including the District of Columbia;

- An estate the income of which is subject to United States federal income tax regardless of its source; or
- A trust (a) if a court within the United States can exercise primary supervision over its administration and one or more United States persons are authorized to control all substantial decisions of the trust or (b) that has a valid election in effect under applicable Treasury Regulations to be treated as a United States person.

If a partnership (including any entity treated as a partnership for United States federal income tax purposes) receives the subscription rights or holds the common stock received upon exercise of the subscription rights or, if applicable, the over-subscription privilege, the tax treatment of a partner in such partnership generally will depend upon the status of the partner and the activities of the partnership. Such a partner or partnership is urged to consult its own tax advisor as to the United States federal income tax consequences of receiving and exercising the subscription rights and acquiring, holding or disposing of our common shares.

EACH RECIPIENT OF RIGHTS IN THE RIGHTS OFFERING SHOULD CONSULT ITS OWN TAX ADVISOR WITH RESPECT TO THE TAX CONSEQUENCES OF THE RIGHTS OFFERING AND THE RELATED SHARE ISSUANCES THAT MAY RESULT FROM SUCH RECIPIENT'S PARTICULAR CIRCUMSTANCES.

The United States federal income tax consequences to a holder of our common stock of the receipt and exercise of subscription rights under the rights offering should be as follows:

Distribution of Subscription Rights

Your receipt of subscription rights pursuant to the rights offering will not be treated as a taxable distribution with respect to your existing shares of common stock for United States federal income tax purposes.

Tax Basis in the Subscription Rights

If the fair market value of the subscription rights you receive is less than 15% of the fair market value of your existing shares of common stock on the date you receive the subscription rights, the subscription rights will be allocated a zero basis for United States federal income tax purposes, unless you elect to allocate your basis in your existing shares of common stock between your existing shares of common stock and the subscription rights in proportion to the relative fair market values of the existing shares of common stock and the subscription rights determined on the date of receipt of the subscription rights. If you choose to allocate basis between your existing shares of common stock and the subscription rights, you must make this election on a statement included with your United States federal income tax return for the taxable year in which you receive the subscription rights. Such an election is irrevocable.

However, if the fair market value of the subscription rights you receive is 15% or more of the fair market value of your existing shares of common stock on the date you receive the subscription rights, then you must allocate your basis in your existing shares of common stock between your existing shares of common stock and the subscription rights you receive in proportion to their fair market values determined on the date you receive the subscription rights. The fair market value of the subscription rights on the date the subscription rights will be distributed is uncertain. In determining the fair market value of the subscription rights, you should consider all relevant facts and circumstances.

Exercise of Subscription Rights

Generally, you will not recognize gain or loss on the exercise of a subscription right received in the rights offering. Your tax basis in a new share of common stock acquired when you exercise a subscription right will be equal to your adjusted tax basis in the subscription right, if any, allocated to the subscription rights, as described above, plus the subscription price paid for the common stock. The holding period of a share of common stock acquired when you exercise your subscription rights will begin on the date of exercise.

Expiration of Subscription Rights

If you allow subscription rights received in the rights offering to expire, you will not recognize any gain or loss for United States federal income tax purposes, and you should re-allocate any portion of the tax basis in your existing shares of common stock previously allocated to the subscription rights that have expired to the existing shares of common stock.

Distributions with Respect to Common Stock Received Upon Exercise of Subscription Rights

Distributions with respect to shares of common stock acquired upon exercise of subscription rights will be taxable as dividend income when actually or constructively received to the extent of our current or accumulated earnings and profits as determined for United States federal income tax purposes. Subject to certain holding period and other requirements, such dividend income will generally be eligible for the dividends received deduction if you are a corporate United States holder and, in the case of dividends paid in taxable years beginning before January 1, 2013, will generally be treated as "qualified dividend income" eligible for reduced rates of taxation if you are a non-corporate United States holder (including an individual). To the extent that the amount of a distribution exceeds our current and accumulated earnings and profits, such distribution will be treated first as a tax-free return of capital, causing a reduction in your adjusted tax basis in such shares of common stock, and the balance in excess of adjusted basis will be taxed as capital gain. We currently do not make any cash distributions on our shares of common stock.

Sale of Common Stock Acquired Upon Exercise of Subscription Rights

If you sell or otherwise dispose of the shares of common stock acquired upon exercise of the subscription rights, you will generally recognize capital gain or loss equal to the difference between the amount realized upon the sale and your adjusted tax basis in the shares of common stock. Your adjusted tax basis in the shares of common stock will generally be equal to your initial tax basis in such shares at the time of the exercise of subscription rights, reduced by adjustments for any distributions with respect to such shares in excess of our current and accumulated earnings and profits (i.e., returns of capital). Such capital gain or loss should be long-term if you have held the shares for more than one year. Generally, long-term capital gains recognized by individuals are taxable at a maximum rate of 15% (scheduled to increase to a maximum rate of 23.8% for taxable years beginning on or after January 1, 2013), and long-term capital gains recognized by corporations are taxable at ordinary corporate tax rates. If you have held your shares for one year or less, your gain or loss on the sale of such shares will be short-term. Short-term capital gains are generally taxed at the rates applicable to ordinary income. Your ability to utilize any capital loss may be subject to

substantial restrictions.

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Information Reporting and Backup Withholding

You may be subject to information reporting and/or backup withholding at a rate of 28% with respect to distributions on or the gross proceeds from the disposition of our common stock. Backup withholding may apply under certain circumstances if you (a) fail to furnish your social security or other taxpayer identification number, which we refer to as "TIN," (b) furnish an incorrect TIN, (c) fail to report interest or dividends properly, or (d) fail to provide a certified statement, signed under penalty of perjury, that the TIN provided is correct, that you are not subject to backup withholding and that you are a United States person. Any amount withheld from a payment under the backup withholding rules is allowable as a credit against (and may entitle you to a refund with respect to) your United States federal income tax liability, provided that the required information is furnished to the IRS. Certain persons are exempt from information reporting and backup withholding, including corporations and financial institutions. You are urged to consult your own tax advisor as to your qualification for exemption from information reporting and backup withholding and the procedure for obtaining such exemption.

CAPITALIZATION

The following table presents our unaudited capitalization and other data as of June 30, 2011 on an actual basis and as adjusted to give effect to the sale by us of _____ shares of common stock in the rights offering at a subscription price of \$[•] per share and after deducting estimated expenses. To the extent the number of shares we sell in the rights offering is fewer than the number herein indicated, our net proceeds will be adjusted in proportion to such change. Please see the section entitled "Use of Proceeds." 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 June 30, 2011	
	Actual	As Adjusted
	(in thousands, except share data)	
Cash, cash equivalents, restricted cash and investments	\$164,814	\$
Long-term debt, net of current portion	\$24,188	\$
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; 337,894,647 shares issued, actual; shares issued, as adjusted	338	
Additional paid-in capital	923,797	
Accumulated deficit	(729,673) (0)
Accumulated other comprehensive gain	71	
Treasury stock, at cost, 217,658 shares	(345) (0)
Total stockholders' equity	194,188	
Total capitalization	\$218,376	\$

The table above excludes 21,113,764 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2011 at a weighted average exercise price of \$2.99 per share, 2,550,900 shares of common stock issuable upon vesting of restricted stock units outstanding as of June 30, 2011 and 7,345,822 shares of common stock available for future grant or issuance under our stock incentive plans as of June 30, 2011.

PLAN OF DISTRIBUTION

On or about [•], 2011, we will distribute the rights, subscription rights certificates and election form, and copies of this prospectus to individuals who owned shares of common stock on the record date. We have not employed any brokers, dealers, or underwriters in connection with the solicitation or exercise of the rights in the rights offering and no commissions, fees or discounts will be paid in connection with the rights offering. While certain of our directors, officers and other employees may solicit responses from you, those directors, officers and other employees will not receive any commissions or compensation for their services other than their normal compensation. If you wish to exercise your subscription rights and purchase shares of common stock, you must complete the subscription rights certificate and return it with payment for the shares to the subscription agent, at the following address:

If Delivering by Mail:

BNY Mellon Shareowner Services
Attn:Corporate Action Department, 27th Floor
P.O. Box 3301
South Hackensack, New Jersey 07606

If Delivering by Hand or Courier:

BNY Mellon Shareowner Services
Attn:Corporate Action Department, 27th Floor
480 Washington Boulevard
Jersey City, New Jersey 07310

In the event that the rights offering is not fully subscribed pursuant to the basic subscription privilege, stockholders who purchased all of the shares available to them pursuant to their basic subscription privilege will have the opportunity to subscribe for unsubscribed rights pursuant to the over-subscription privilege. Please see the section entitled "The Rights Offering."

Pursuant to the terms of our securities purchase agreement with Invus, L.P., as amended and supplemented, Invus is required to exercise its basic subscription privilege in full and purchase at least _____ shares of our common stock in the rights offering, subject to certain customary closing conditions. We do not know of any other existing agreements between any stockholder, broker, dealer, underwriter, or agent relating to the sale or distribution of the common stock underlying the rights.

If you have any questions, you should contact us at:

Investor Relations
Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Place
The Woodlands, Texas 77381-1160
Telephone: (281) 863-3000

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 reports on Form 10-Q for the quarterly periods ended March 31 and June 30, 2011;
- our current reports on Form 8-K dated February 23, April 28 and August 12, 2011, our current report on Form 8-K/A dated July 30, 2010 and filed on March 16, 2011 and our current report dated April 28, 2011 and filed on August 9, 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. Unless specifically stated to the contrary, none of the information that we disclose under Items 2.02 or 7.01 of any Current Report on Form 8-K that we have from time to time furnished to the SEC will be incorporated by reference into, or otherwise included in, this prospectus.

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
Subscription Agent and Information Agent Fees	25,000
Transfer Agent and Registrar Fees	3,000
Miscellaneous Expenses	3,780
Total	\$205,000

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
3.1	Restated Certificate of Incorporation (filed as Exhibit 3.1 to the Company's Registration Statement on Form S-1 (Registration No. 333-96469) and incorporated by reference herein).
3.2	First Certificate of Amendment to Restated Certificate of Incorporation (filed as Exhibit 3.2 to the Company's Annual Report on Form 10-K for the period ended December 31, 2007 and incorporated by reference herein).
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4.2	Amendment, dated October 7, 2009, to Securities Purchase Agreement, dated June 17, 2007, with Invus, L.P. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated October 7, 2009 and incorporated by reference herein).
4.3	Registration Rights Agreement, dated June 17, 2007, with Invus, L.P. (filed as Exhibit 10.3 to the Company's Current Report on Form 8-K dated June 17, 2007 and incorporated by reference herein).
4.4	Supplement to Transaction Agreements, date March 15, with Invus, L.P. and Invus C.V. (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated March 15, 2010 and incorporated by reference herein).
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*5.1	Opinion of Vinson & Elkins L.L.P.
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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 — Form of Amendment to Stock Option Agreements and Restricted Stock Unit Agreements with Officers under the Equity Incentive Plan (filed as Exhibit 10.1 to the Company's Current Report on Form 8-K dated August 12, 2011 and incorporated by reference herein).
- †10.22 — 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).

†10.23 — 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).

†10.24 — 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).

†10.25	—	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).
†10.26	—	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).
10.27	—	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).
10.28	—	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).
10.29	—	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).
10.30	—	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).
10.31	—	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).
*99.1	—	Form of Instructions for Use of Subscription Rights Certificate and Election Form.
*99.2	—	Form of Notice of Guaranteed Delivery.
*99.3	—	Form of Letter to Record Stockholders.
*99.4	—	Form of Letter to Nominee Holders.
*99.5	—	Form of Letter to Clients of Nominee Holders.
*99.6	—	Form of Beneficial Owner Election Form.
*99.7	—	Form of Nominee Holder Certification.

† 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 Reports on Form 10-Q for the periods ended March 31 and June 30, 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

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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 August 12, 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)	August 12, 2011
* Jeffrey L. Wade	Executive Vice President, Corporate Development and Chief Financial Officer (principal financial officer)	August 12, 2011
* James F. Tessmer	Vice President, Finance and Accounting (principal accounting officer)	August 12, 2011
* Samuel L. Barker, Ph.D.	Chairman of the Board of Directors	August 12, 2011
* Philippe J. Amouyal	Director	August 12, 2011
* Raymond Debbane	Director	August 12, 2011
* Robert J. Lefkowitz, M.D.	Director	August 12, 2011
* Alan S. Nies, M.D.	Director	August 12, 2011
* Frank P. Palantoni	Director	August 12, 2011
* Christopher J. Sobecki	Director	August 12, 2011
* Judith L. Swain, M.D.	Director	August 12, 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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