



2009 Annual Report

*Discovering Breakthrough Treatments
for Human Disease*

To Our Shareholders,

In two thousand nine, Lexicon achieved significant progress in each of its four major clinical programs. We reported our first positive proof-of-concept clinical data from our LX1031 program for non-constipating irritable bowel syndrome. We successfully completed a Phase 2 study with LX4211 in patients with type 2 diabetes mellitus and initiated Phase 2 studies in patients with both LX2931 and LX1032, for rheumatoid arthritis and carcinoid syndrome, respectively. Lexicon also achieved several other important clinical, preclinical, and research milestones—further advancing our pipeline of new drug candidates.

A Highly Productive Drug Discovery Engine

On the backdrop of a worldwide economic crisis, we remain determined to accomplish our goals to bring forward new drug candidates with breakthrough potential. Relative to many other companies, Lexicon has remained financially stable during this last year and successfully raised over \$55 million through a public offering of common stock, strengthening our financial position and enhancing our ability to move forward with our clinical programs. Concurrently, we concentrated our human and financial resources on key drug discovery programs that we could efficiently advance through the clinic. Our productive drug discovery engine continues to advance exciting new candidates, and we have witnessed remarkable results in Phase 2 trials conducted to date. Our sound strategy, our dedicated employees, and our very promising pipeline put us on a path to ultimately recognize the benefits of bringing potential breakthrough therapies to patients in areas of significant unmet medical need.

Key Clinical Developments

LX4211 for type 2 diabetes mellitus is a once-daily, oral small molecule dual inhibitor of the sodium-glucose cotransporters, SGLT1 and SGLT2, which completed Phase 1 and 2a clinical trials this year. Top-line results from the Phase 2a clinical trial of LX4211 (reported January 2010)

demonstrated highly statistically significant and rapid improvements in multiple parameters in type 2 diabetic patients, including improvements in several parameters of glycemic control, with remarkable reductions in HbA1c within four weeks. Importantly, LX4211 also showed favorable safety, cardiovascular and metabolic profiles in this study. LX4211 is not only Lexicon's second clinical program to show positive proof-of-concept data but could have a potential "best-in-class" profile among other type 2 diabetes drugs.

LX1031 for non-constipating irritable bowel syndrome is an orally-administered small molecule that acts locally in the gastrointestinal tract to reduce serotonin synthesis. Top-line results from our Phase 2a study showed that treatment with LX1031 produced a statistically significant improvement in a global assessment of relief of IBS pain and discomfort over the four-week dosing period. Improvements in the global assessment corresponded with statistically significant improvements in stool consistency. Notably, increased clinical response correlated with a greater reduction in serotonin synthesis as reflected by measures of urinary 5-HIAA, a breakdown product of serotonin. This important finding enables future development to be guided by a biomarker with direct mechanistic and clinical relevance.

LX2931 for autoimmune disorders such as rheumatoid arthritis is an orally-delivered small molecule inhibitor of sphingosine-1-phosphate (S1P) lyase, the enzyme responsible for the irreversible breakdown of S1P, an important

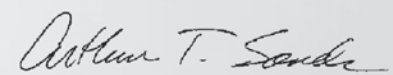
immuno-active signalling molecule. Lexicon completed Phase 1 clinical trials of this drug candidate, as well as an important drug-drug interaction study with methotrexate in patients with rheumatoid arthritis. In clinical trials conducted to date, a dose-dependent reduction in circulating lymphocytes has been observed, confirming the mechanism of action of LX2931 in regulating the immune system. Lexicon initiated a Phase 2a study in patients with rheumatoid arthritis at sites in the United States and Europe that is expected to be completed around the end of the year.

LX1032 for symptoms associated with carcinoid syndrome is a peripherally-acting, orally-administered small molecule inhibitor of serotonin synthesis that does not cross the blood-brain barrier. Lexicon initiated a Phase 2a clinical trial of this drug candidate in patients with carcinoid syndrome in the United States, and will soon initiate a separate Phase 2a trial in Europe; these studies are expected to be completed in the second half of 2010. We received orphan drug designation from the Committee for Orphan Medical Products of the European Medicines Agency for development of LX1032, in addition to the previous year's Fast Track designation from the FDA.

The Path Forward to Breakthrough Treatments

In 2010, we are looking forward to a very exciting year where we will see important proof-of-concept results in areas of significant unmet medical need translate into both drug development and business milestones. Our broad and deep preclinical pipeline is the foundation on which we continue to build for our future success. As ever, we remain focused on our mission: to discover breakthrough treatments for human disease.

Thank you for joining us on this exciting journey through the genome and into drug discovery and development. I look forward to updating you on our progress this year.



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

Corporate Information

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Annual Report

Our 2009 annual report on Form 10-K is available, without charge, upon request by contacting our Investor Relations Department at 281-863-3000.

Annual Meeting

Our annual meeting of shareholders will be held at 8:00AM CDT on April 29, 2010 at Lexicon's corporate headquarters, 8800 Technology Forest Place, The Woodlands, Texas 77381.

This annual report to shareholders contains forward-looking statements, including statements relating to Lexicon's regulatory filings, clinical and preclinical development programs and the potential therapeutic and commercial potential of the drug candidates in those programs. These statements involve risks, uncertainties and other important factors that may cause the actual results of Lexicon to be materially different from any future results expressed or implied by such forward-looking statements. Information identifying such risks, uncertainties and other important factors is contained in the sections entitled "Factors Affecting Forward-Looking Statements" and "Risk Factors" in our annual report on Form 10-K for the year ended December 31, 2009, as filed with the Securities and Exchange Commission and included as part of this annual report to shareholders.

Executive Officers

Arthur T. Sands, M.D., Ph.D.

President and Chief Executive Officer

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Jeffrey L. Wade, J.D.

*Executive Vice President and
General Counsel*

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*Executive Vice President and
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*Senior Vice President,
Clinical Development*

Steven A. Tragash

Senior Vice President of Corporate Affairs

James F. Tessmer

Vice President, Finance and Accounting

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Projects, Inc.; Former President, U.S.
Pharmaceutical Group, Bristol-Myers
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*Managing Director,
The Invus Group, LLC*

Raymond Debbane

*President and Chief Executive Officer,
The Invus Group, LLC*

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Institute and James B. Duke Professor
of Medicine and Professor of
Biochemistry, Duke University
Medical Center*

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*Former Global President and
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Products Company*

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Lexicon Pharmaceuticals, Inc.*

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The Invus Group, LLC*

Judith L. Swain, M.D.

*Executive Director, Singapore Institute
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Professor of Medicine at the National
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