



Lexicon to Present Preclinical IN VIVO Efficacy Data Demonstrating Ability of New Investigational Compound to Enhance and Maintain Semaglutide-Promoted Weight Loss

November 4, 2024

Investigational New Drug (IND) application planned in 2025 for LX9851, a first-in-class, potent, selective, orally bioavailable molecule, as an anti-obesity agent

Data from Lexicon's Obesity Week presentations summarize the preclinical efficacy and mechanism of action of LX9851

THE WOODLANDS, Texas, November 4, 2024 -- Lexicon Pharmaceuticals, Inc. (Nasdaq: LXRX) today announced it will present data from two studies related to LX9851, its investigational compound for obesity and weight loss, at Obesity Week 2024, November 3-5, 2024, at the Henry B. Gonzalez Convention Center in San Antonio, Texas.

Preclinical *in vivo* efficacy data from the first study showed that treatment with LX9851 resulted in significant reductions in weight, food intake and fat mass in diet-induced obese (DIO) mice. Among other important findings, LX9851 mitigated weight regain following discontinuation of the GLP-1 analogue semaglutide. This study ("First-in-Class ACSL5i LX9851 Enhances and Maintains Semaglutide-Promoted Weight Loss in DIO Mice") investigated the body-weight reduction and weight maintenance effects of Lexicon's first-in-class small molecule ACSL5 inhibitor, as a monotherapy and in combination with semaglutide, in a DIO mouse model. On Day 28, fat and lean body mass were measured by DEXA (OsteoSys body analyzer). All treatments with LX9851 resulted in a reduction in fat mass compared to vehicle control. The greatest weight reduction with no significant effect on lean body mass was observed when LX9851 was combined with semaglutide. The combination therapy also resulted in additive positive effects on liver steatosis and related study end points.

Preclinical *in vivo* efficacy data from the second study characterized the novel mechanism of action of LX9851. Previous research demonstrated that free fatty acids in the small intestine drive the release of GLP-1 and other gut hormones, which delays gastric emptying and ultimately lowers the desire for additional food consumption. This series of neural relays creates satiety, the feeling of fullness after consuming food, and is known as the ileal brake. This study ("Acsl5 KO and an Oral ACSL5 Inhibitor Lower High Fat Diet Intake in Mice by Activating the Ileal Brake") demonstrated that inhibition of ACSL5, either through genetic knockout of the gene or pharmacological inhibition of the enzyme in wildtype mice, activates the ileal brake.

"Data presented during Obesity Week reinforces our optimism for LX9851. We believe that these promising findings, along with other ongoing research, will provide robust evidence to support our planned Investigational New Drug Application (IND) filing with FDA for LX9851 in 2025," said Alan Main, Ph.D., Executive Vice President, Innovation and Chemical Sciences.

Details for the presentations are as follows:

- **First-in-Class ACSL5i LX9851 Enhances and Maintains Semaglutide-Promoted Weight Loss in DIO Mice** -- a moderated poster presentation (Poster # 634), Tuesday, November 5, 2:30-3:30p.m. CT Exhibit Hall 4, presented by Patricia McDonald, Ph.D., Senior Director, Biology, Lexicon Pharmaceuticals Inc.
- **Acsl5 KO and an Oral ACSL5 Inhibitor Lower High Fat Diet Intake in Mice by Activating the Ileal Brake** – a moderated poster presentation (Poster #006), Sunday, November 3, 7:30-8:30 p.m. CT, Exhibit Hall 4 presented by David Powell, Scientific Advisor, Lexicon Pharmaceuticals

About LX9851

LX9851 is an orally delivered small molecule drug candidate for the treatment of obesity and associated cardiometabolic disorders. We are investigating the pharmacology of LX9851 as a stand-alone therapy and in combination with GLP-1 agonists such as semaglutide. We anticipate filing an Investigational New Drug application with the U.S. Food and Drug Administration (FDA) in 2025, followed by the initiation of clinical development. Our scientists identified ACSL5, the target of LX9851, based on their discovery that knockout mice lacking the target enzyme exhibited favorable phenotypes across multiple measures of metabolic syndrome in preclinical models, including resistance to diet-induced obesity and improved body composition.

About Lexicon Pharmaceuticals

Lexicon is a biopharmaceutical company with a mission of pioneering medicines that transform patients' lives. Through the Genome5000™ program, Lexicon's unique genomics target discovery platform, Lexicon scientists studied the role and function of nearly 5,000 genes and identified more than 100 protein targets with significant therapeutic potential in a range of diseases.

Through the precise targeting of these proteins, Lexicon is pioneering the discovery and development of innovative medicines to treat disease safely and effectively. Lexicon has commercially launched one of these medicines, INPEFA® (sotagliflozin) in the United States, and has a pipeline of other promising drug candidates in discovery and clinical and preclinical development in neuropathic pain, diabetes and metabolism and other indications. For additional information, please visit www.lexpharma.com.

Safe Harbor Statement

This press release contains “forward-looking statements,” including statements relating to Lexicon’s financial position and long-term outlook on its business, growth and future operating results, discovery and development of products, strategic alliances and intellectual property, as well as other matters that are not historical facts or information. All forward-looking statements are based on management’s current assumptions and expectations and involve risks, uncertainties and other important factors, specifically including Lexicon’s ability to meet its capital requirements, successfully commercialize its approved products, conduct preclinical and clinical development and obtain necessary regulatory approvals of LX9851 and its other drug candidates on its anticipated timelines, achieve its operational objectives, obtain patent protection for its discoveries and establish strategic alliances, as well as additional factors relating to manufacturing, intellectual property rights, and the therapeutic or commercial value of its drug candidates. Any of these risks, uncertainties and other factors may cause Lexicon’s actual results to be materially different from any future results expressed or implied by such forward-looking statements. Information identifying such important factors is contained under “Risk Factors” in Lexicon’s annual report on Form 10-K for the year ended December 31, 2023 and other subsequent disclosure documents filed with the Securities and Exchange Commission. Lexicon undertakes no obligation to update or revise any such forward-looking statements, whether as a result of new information, future events or otherwise.

For Investor and Media Inquiries:

Lisa DeFrancesco
Lexicon Pharmaceuticals, Inc.
lexinvest@lexpharma.com