Lexicon Pharmaceuticals Announces Publication of Preclinical Data in the Journal of the Endocrine Society on Acyl-CoA Synthetase 5 (ACSL5) Reinforcing the Scientific Rationale for LX9851

December 10, 2025

THE WOODLANDS, Texas, Dec. 10, 2025 (GLOBE NEWSWIRE) -- Lexicon Pharmaceuticals, Inc. (Nasdaq: LXRX) today announced the publication of preclinical data validating Acyl-CoA Synthetase 5 (ACSL5) as a target for obesity and chronic weight management. The paper, titled “Acyl-CoA Synthetase 5 knockout and inhibitors protect against diet-induced obesity in mice by activating the ileal brake,” was published online in the *Journal of the Endocrine Society*.

ACSL5 is an enzyme encoded by the *Acsl5* gene that plays a vital role in lipid metabolism and is the target of LX9851, the Company’s investigational non-incretin, oral, small molecule ACSL5 inhibitor. Animal model data showed that mice genetically modified to lack the ACSL5 gene exhibited favorable metabolic characteristics, including reduced body fat and conserved lean body mass.

In March 2025, Lexicon entered into an exclusive, worldwide licensing agreement for LX9851 with Novo Nordisk.

“These preclinical findings validate our strategy of targeting ACSL5 for the development of new therapeutic options for people in need of obesity and weight management treatment and support the clinical advancement of LX9851,” said Craig Granowitz, M.D., Ph.D., Lexicon’s senior vice president and chief medical officer. “We see an opportunity for LX9851 to build on the success of incretin-based therapies as the obesity treatment landscape continues to evolve. With a novel mechanism, oral administration, strong preclinical results and possibility for both monotherapy and combination applications, we feel LX9851 has the potential to occupy a unique space in the treatment landscape for obesity and metabolic conditions. We look forward to continuing the work with Novo Nordisk to maximize the potential of this innovative medicine.”

Preclinical Research Findings
Lexicon scientists generated mice with the ACSL5 gene deleted (knocked out) globally. These ACSL5 knockout mice had lower body fat, triglycerides, total cholesterol, and blood glucose as well as conserved lean body mass compared with mice carrying the ACSL5 gene. Additionally, ACSL5 knockout mice had lower body weight and body fat while maintaining their lean body mass when fed a high-fat diet. Similar effects were also observed when potent, small molecule inhibitors of ACSL5 were administered orally to mice with diet-induced obesity. Mechanistic studies demonstrated that the favorable metabolic characteristics observed were by activating the ileal brake mechanism which delayed gastric emptying and decreased food consumption.

About LX9851
LX9851 is a first-in-class, non-incretin, oral, small molecule inhibitor of acyl-CoA synthetase 5 (ACSL5) for the treatment of obesity and associated cardiometabolic disorders. Lexicon scientists identified the function of 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. Lexicon has investigated the pharmacology of LX9851 as a stand-alone therapy and in combination with GLP-1 agonists such as semaglutide.

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 safely and effectively treat disease. Lexicon has advanced multiple medicines to market and has a pipeline of promising drug candidates in discovery and clinical and preclinical development in heart failure, neuropathic pain, obesity, cardiology, diabetes 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, including the commercialization of its approved products and the clinical development of, regulatory filings for, and potential therapeutic and commercial potential of LX9851 and its other drug candidates. In addition, this press release also contains forward looking statements relating to Lexicon’s growth and future operating results, discovery, development and commercialization 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, successfully conduct preclinical and clinical development and obtain necessary

regulatory approvals of 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 approved products and other 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, 2024, as 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.

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