Lexicon's LX9211 Shows Significant and Consistent Benefits in the Treatment of Painful Diabetic Neuropathy in Full Results from the Phase 2 RELIEF-DPN-1 Trial Presented at the 16th Annual Pain Therapeutics Summit

November 15, 2022

- Achieved primary endpoint for reduction in average daily pain score (ADPS) at week 6
- Significant benefits demonstrated on burning pain and on pain interference with sleep
- No evidence of withdrawal symptoms or rebound pain after treatment ended

Conference Call and Webcast Today at 5:00pm ET Hosted by Lexicon Management

The Woodlands, Texas, November 14, 2022 - Lexicon Pharmaceuticals, Inc. (Nasdaq: LXRX) today announced that full results from the RELIEF-DPN-1 trial of its investigational drug LX9211 were presented at the 16th Annual Pain Therapeutics Summit in Washington, D.C. The oral presentation, titled "*A Phase 2 Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN-1)*," was delivered at 3:35pm ET today.

"LX9211 achieved the primary objective of this study by reducing patients' average daily pain," said Dr. Anand Patel, the Chief Medical Officer at Conquest Research, a principal investigator in the RELIEF-DPN-1 trial, and presenter of the results. "These final data demonstrate additional positive effects of LX9211 on measures that are very meaningful to patients suffering from painful diabetic neuropathy, including burning pain and sleep interference, which have direct impact on patient quality of life."

Today's presentation of full data from the entire 11-week evaluation period, which included a 5-week placebo run-off period following the initial 6-week treatment period, showed consistent and statistically significant treatment-period benefits in measures of particular importance in painful diabetic neuropathy (also known as diabetic peripheral neuropathic pain) for both dose arms compared to placebo, such as a reductions in burning pain ($p<0.001$ and $p=0.017$, respectively) and interference of pain in sleep ($p=0.005$ and $p=0.002$, respectively).

During the blinded 5-week placebo run-off period, there was a gradual tapering of efficacy in both treatment arms with no evidence of rebound pain or withdrawal symptoms. There were no observed differences in treatment-emergent adverse events between the treatment and placebo arms during the run-off period, and no drug-related serious adverse events or deaths were reported in the trial.

In topline results previously reported in June 2022, LX9211 achieved the primary endpoint of the trial by demonstrating a statistically significant reduction from baseline in average daily pain score (ADPS) at week 6 compared to placebo in the low dose arm (100 mg initial single dose, followed by 10 mg daily doses), and narrowly missed statistical significance in the high dose arm (200 mg initial single dose, followed by 20 mg daily doses).

"These results further support AAK1's utility as a potential new mechanism of action for neuropathic pain and the rapid advancement of LX9211 into phase 3 development in painful diabetic neuropathy, which we are planning to initiate in 2023," said Dr. Craig Granowitz, Lexicon's senior vice president and chief medical officer.

About Today's Live Conference Call and Webcast

Following Dr. Patel's presentation, he will join Lexicon management on a live conference call and webcast at 5:00pm ET to discuss the study results. The dial-in number for the conference call is 888-886-7786 and the conference ID for all callers is 28989106. The live webcast and replay may be accessed by visiting Lexicon's website at www.lexpharma.com/events. An archived version of the webcast will be available on the website for 14 days.

About the RELIEF-DPN-1 Study

RELIEF-DPN-1 was a Phase 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating the efficacy, safety and pharmacokinetics of LX9211 in the treatment of painful diabetic neuropathy, also referred to as diabetic peripheral neuropathic pain. The study enrolled 319 patients at 45 U.S. clinical sites, evaluating three treatment groups receiving placebo or one of two dosing regimens of LX9211 (an initial single dose of 100 mg followed by once-daily doses of 10 mg or an initial single dose of 200 mg followed by once-daily doses of 20 mg). The primary efficacy endpoint under evaluation was the change from baseline to week 6 in ADPS, based on the 11-point numerical rating scale. The results of the study on the primary endpoint showed a reduction from baseline in ADPS of 1.39 points ($p=0.007$ versus placebo) in the low dose arm and 1.27 points ($p=0.030$ versus placebo) in the high dose arm, compared to 0.72 in the placebo arm. Under the statistical analysis plan for the

study, a p-value of less than 0.028 was considered statistically significant.

The RELIEF-DPN-1 study was the first of two Phase 2 proof-of-concept studies evaluating LX9211 in neuropathic pain. LX9211 is also under evaluation in RELIEF-PHN-1, a study in patients with post-herpetic neuralgia, from which Lexicon is targeting top-line results around the end of the fourth quarter of 2022.

About LX9211

Discovered using Lexicon's unique approach to gene science, LX9211 is a potent, orally delivered, selective small molecule inhibitor of adaptor-associated kinase 1 (AAK1). Lexicon identified AAK1 in its target discovery efforts as a promising approach for the treatment of neuropathic pain and identified LX9211 and another development candidate in a neuroscience drug discovery alliance with Bristol-Myers Squibb from which Lexicon holds exclusive development and commercialization rights. Preclinical studies of LX9211 demonstrated central nervous system penetration and reduction in pain behavior in models of neuropathic pain without affecting opiate pathways. LX9211 has received Fast Track designation from the U.S. Food and Drug Administration for the development in diabetic peripheral neuropathic pain.

About Lexicon Pharmaceuticals

Lexicon is a biopharmaceutical company with a mission of pioneering medicines that transform patients' lives. Through its Genome5000™ program, 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 advanced one of these medicines to market and has a pipeline of promising drug candidates in discovery and clinical and preclinical development in heart failure, 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 the clinical development of, regulatory filings for and potential therapeutic and commercial potential of LX9211. In addition, this press release also contains forward looking statements relating to the clinical development of, regulatory filings for and potential therapeutic and commercial potential of sotagliflozin and Lexicon's other potential drug candidates, as well as 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 conduct preclinical and clinical development and obtain necessary regulatory approvals of sotagliflozin, LX9211 and its other potential drug candidates on its anticipated timelines, successfully commercialize any products for which it obtains regulatory approval, 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, 2021, 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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