Lexicon Pharmaceuticals Announces Topline Results from Phase 2b PROGRESS Study Evaluating Pilavapadin (LX9211) in Adults with Diabetic Peripheral Neuropathic Pain

March 3, 2025

Pilavapadin achieved meaningful pain reduction versus placebo and was well-tolerated in the 10 mg dose, meeting the Company's objectives for the study

Advancement of 10 mg dose into Phase 3 development in DPNP supported by both PROGRESS and RELIEF DPN-1 studies, which collectively enrolled approximately 600 pilavapadin-treated patients

Conference call and webcast at 8:00 a.m. ET

THE WOODLANDS, Texas, March 03, 2025 (GLOBE NEWSWIRE) -- Lexicon Pharmaceuticals, Inc. (Nasdaq: LXRX) today announced topline results from the PROGRESS Phase 2b study evaluating pilavapadin (LX9211), an oral, non-opioid investigational adaptor-associated kinase 1 (AAK1) inhibitor in adult patients with moderate to severe diabetic peripheral neuropathic pain (DPNP).

Lexicon's objective for the PROGRESS study was to identify a dose exhibiting meaningful pain reduction and improved tolerability compared to that observed in the previous Phase 2 RELIEF-DPN-1 study. All objectives for the PROGRESS study were achieved with respect to the 10 mg dose, which Lexicon has identified as the appropriate dose to advance into Phase 3 development based both on these PROGRESS results and the previous results from RELIEF DPN-1. In RELIEF-DPN-1, dosing regimens utilized a ten-fold loading dose on Day 1 and the 100 mg/10 mg dose arm, but not the 200 mg/20 mg dose arm, achieved significantly reduced pain scores as compared to both baseline and placebo, with the loading dose affecting tolerability in both treatment arms. The PROGRESS study removed the Day 1 loading dose and examined single daily doses of 10 mg, 20 mg for one week followed by 10 mg, and 20mg.

In the PROGRESS study, all pilavapadin treatment arms demonstrated reductions in the mean average daily pain score (ADPS) from baseline to Week 8 with the 10 mg, 20 mg/10 mg and 20 mg dose arms achieving reductions of 1.74, 1.70 and 1.38, respectively, compared to a reduction of 1.31 in the placebo arm. The study's statistical analysis plan was designed to detect a dose-response signal based on a prespecified model that assumed separation of all treatment arms from placebo when measuring the primary endpoint of change from baseline to Week 8 on ADPS as compared to placebo. As a result of the lack of separation in ADPS reduction between the 20 mg dose arm and placebo, the study results did not reach statistical significance on the primary endpoint (p=0.11). However, the 10 mg dose arm demonstrated clear evidence of effect by achieving early and clinically meaningful separation from placebo on ADPS that was maintained throughout the study duration.

Adverse events were more frequent in the pilavapadin treatment arms, but were significantly improved from the RELIEF-DPN-1 study across all doses. Nearly all adverse events were reported as mild or moderate. Adverse events were most prominent at the 20 mg dose and pilavapadin was generally well-tolerated at the 10 mg dose. Dizziness and nausea were the most commonly reported adverse events and the most frequently associated with patient discontinuations from the study, which occurred most predominantly in the 20 mg dose.

On the basis of the PROGRESS study results in the 10 mg dose arm, together with the previous findings from RELIEF-DPN-1, Lexicon has identified 10 mg once daily as an appropriate dose to advance into Phase 3 clinical development for DPNP.

"DPNP is a complex and highly prevalent complication of diabetes which severely impacts quality of life. People with DPNP often cycle through multiple treatments without adequate relief, and they and their health care providers are in dire need of new, non-opioid treatment options," said Rodica Pop-Busui M.D., Ph.D., Jordan Schnitzer Chair in Diabetes, Professor of Medicine and Division Head, Endocrinology, Diabetes and Clinical Nutrition Director, Harold Schnitzer Diabetes Center, Oregon Health & Science University and lead investigator of the PROGRESS study. "The results of the PROGRESS 2b study provide further evidence that AAK1 inhibition may provide an alternative treatment option to opioid use, offering clinically meaningful reductions in pain and the potential for pilavapadin to fill a critical gap in DPNP care."

"We are very encouraged by the topline results from the PROGRESS Phase 2b study, which give us great confidence in Phase 3 development of the 10 mg dose for DPNP," said Mike Exton, Ph.D., chief executive officer and director of Lexicon. "The neuropathic pain market represents a multibillion-dollar opportunity that is primed for innovative treatments. With these results, we firmly believe that pilavapadin has the opportunity to become the first oral non-opioid treatment approved in neuropathic pain in 20 years. The enormous potential of this investigational medicine has generated significant interest from potential partners, and we

intend to accelerate these discussions while we plan for Phase 3 development."

A full analysis of the results of the PROGRESS study will be submitted for presentation at a forthcoming medical conference and for publication in a peer-reviewed journal.

Conference Call and Webcast Information
Lexicon management will hold a live conference call and webcast today at 8:00 a.m. ET / 7:00 a.m. CT to review the details of this announcement. Participants can access the conference call live via webcast on the Events page of the Company's website at https://investors.lexpharma.com/. Participants who wish to ask a question may register here to receive dial-in numbers and a unique pin to join the call. An archived version of the webcast will be available on the Lexicon website.

About the PROGRESS Study
The PROGRESS study commenced in December 2023 and enrolled 496 adult patients with a diagnosis of diabetes (type 1 or type 2) and moderate to severe DPNP. The study was placebo-controlled with a primary endpoint of change from baseline to Week 8 in ADPS as compared to placebo and evaluated three treatment groups receiving once daily pilavapadin doses of 10 mg, 20 mg or 20 mg for seven days followed by 10 mg thereafter. Secondary endpoints included change from baseline to Week 8 in burning pain and pain interference on sleep. Study design permitted patients to remain on one stable-dose DPNP therapy (e.g. gabapentin, pregabalin or duloxetine) without withdrawing from therapies that, although inadequate, may be providing some benefit – aligning with how new DPNP drugs are likely to be used in practice.

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 pilavapadin in the treatment of DPNP. The study enrolled 319 patients at 45 U.S. clinical sites, evaluating three treatment groups receiving placebo or one of two dosing regimens of pilavapadin (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.

About Diabetic Peripheral Neuropathic Pain (DPNP)
DPNP is a debilitating chronic complication of diabetes which can result in burning pain, numbness, and other symptoms in the hands, feet, legs and arms. There are approximately 9 million patients in the U.S. who are suffering with DPNP.

About Pilavapadin
Discovered using Lexicon's unique approach to gene science, pilavapadin (LX9211) is a potent, once-daily, orally delivered, selective, investigational small molecule inhibitor of AAK1, a novel target for neuropathic pain which inhibits reuptake and recycling of neurotransmitters involved in pain signaling without affecting opiate pathways. Lexicon identified AAK1 in its target discovery efforts as a promising approach for the treatment of neuropathic pain. Preclinical studies of pilavapadin demonstrated central nervous system penetration and reduction in pain behavior in models of neuropathic pain without affecting opiate pathways.

The efficacy, safety and pharmacokinetics of pilavapadin in DPNP were also evaluated in the Phase 2a proof-of-concept RELIEF-DPN-1 study, which met the primary endpoint of reducing ADPS at Week 6 compared to placebo and demonstrated substantial and consistent benefits in addressing DPNP symptoms, including burning pain and pain interference on sleep. Pilavapadin has received Fast Track designation from the U.S. Food and Drug Administration for development in DPNP.

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 the clinical development and results of, regulatory filings for and potential therapeutic and commercial potential of pilavapadin (LX9211). In addition, this press release also contains forward-looking 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 conduct preclinical and clinical development and obtain necessary regulatory approvals of pilavapadin, LX9851, sotagliflozin 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.

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