Xenon Pharmaceuticals Announces Positive Topline Results from Phase 2b 'X-TOLE' Clinical Trial of XEN1101 for the Treatment of Focal Epilepsy

October 4, 2021

All Primary and Secondary Seizure Reduction Endpoints Statistically Significant Across All Dose Groups, with p-value of <0.001 for 20 mg and 25 mg Dose Groups

Xenon to Host Conference Call and Live Webcast Today at 7:30 am Eastern Time

BURNABY, British Columbia, Oct. 04, 2021 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE), a neurology-focused biopharmaceutical company, today reported positive topline results from the Phase 2b X-TOLE clinical trial, which evaluated the clinical efficacy, safety, and tolerability of XEN1101 – a differentiated Kv7 potassium channel modulator – administered as adjunctive treatment in adult patients with focal epilepsy.

The trial met its primary efficacy endpoint with XEN1101 demonstrating a statistically significant and dose-dependent reduction from baseline in monthly (defined as 28 days) focal seizure frequency when compared to placebo (monotonic dose response; p<0.001). Additional primary and secondary measures included a pairwise comparison of each active dose to placebo and a responder analysis with the proportion of patients who achieved a 50% or greater reduction in monthly focal seizure frequency from baseline. These results are shown in the following table; all p-values are 2-sided comparing the active dose to placebo:

	XEN1101 25 mg (N=112)	**XEN1101 20 mg (N=51)**	**XEN1101 10mg (N=46)**	**Placebo (N=114)**
Median Reduction from Baseline in Monthly Focal Seizure Frequency	52.8% (p<0.001)	46.4% (p<0.001)	33.2% (p=0.035)	18.2%
Patients with at least a 50% Reduction in Monthly Focal Seizure Frequency from Baseline	54.5% (p<0.001)	43.1% (p<0.001)	28.3% (p=0.037)	14.9%

Jacqueline A. French, MD, Professor in the Department of Neurology at NYU Langone Health and Co-director of Epilepsy Clinical Trials at NYU Langone's Comprehensive Epilepsy Center; Founder/Director of the Epilepsy Study Consortium; and Chair of the XEN1101 X-TOLE Steering Committee, stated, "Many patients today are living with the debilitating impacts of focal seizures, even while taking multiple anti-seizure medications, so there is a substantial need for new, efficacious and well-tolerated therapies. The X-TOLE results generated from this large, multicenter, controlled trial are truly exciting because they demonstrate impressive efficacy of XEN1101 for adult patients with focal epilepsy, including those with seizures that are deemed difficult to treat. In addition, physicians and patients could benefit from XEN1101's other important attributes, such as once-a-day dosing in the evening with no titration. With its unique potassium channel mechanism-of-action, the strength of these topline data suggest XEN1101 could play an important role in treating focal epilepsy."

Dr. Christopher Kenney, Xenon's Chief Medical Officer commented, "On behalf of the entire Xenon team, I wish to extend our thanks to the patients, investigators, and site coordinators who participated in the X-TOLE study. We have generated strong evidence that supports the efficacy, safety and tolerability of XEN1101 and depicts a highly favorable product profile for XEN1101. Importantly, we saw statistically significant reductions of focal onset seizures compared to placebo across all dose groups, which suggests it is highly active in the central nervous system. With these compelling topline results, we are eager to work with the FDA to plan for an expedited development path moving forward."

Designed as a randomized, double-blind, placebo-controlled, multicenter study, the Phase 2b X-TOLE clinical trial evaluated the clinical efficacy, safety, and tolerability of XEN1101 administered as once-daily adjunctive treatment in adult patients with focal epilepsy. The study included a total of 325 randomized and treated subjects in the safety population and 323 subjects in the modified intent to treat population for the efficacy analyses. Subjects had an average age of 40.8 ± 13.3 years, and 8.9%, 40.3%, or 50.8% of the subjects were on and continued taking one, two, or three stable background anti-seizure medications (ASMs) throughout the study, respectively, and failed a median of 6 previous ASMs prior to study entry. The median baseline seizure frequency across the study groups was approximately 13.5 per month. Of the 285 subjects who completed the double-blind period, 96.5% entered the open-label extension to evaluate the long-term safety, tolerability, and effectiveness of XEN1101.

Summary of Results

Key Efficacy Findings:

- The primary objective of the study was to assess the dose response trend of XEN1101 in reducing monthly focal seizure

frequency, based on a ranked ANCOVA model. The median percent reduction in monthly focal seizure frequency was 52.8% in the XEN1101 25 mg group, 46.4% in the XEN1101 20 mg group, and 33.2% in the XEN1101 10 mg group compared to 18.2% in the placebo group. The monotonic dose response relationship between the XEN1101 active dose groups compared to placebo was statistically significant (p<0.001). These data demonstrated a highly statistically significant dose-response relationship for XEN1101 in the adjunctive treatment of focal seizures in adult patients with a history of difficult-to-treat seizures.

- In addition, XEN1101 demonstrated a statistically significant reduction from baseline in monthly focal seizure frequency in pairwise comparisons to placebo for all three XEN1101 doses. The median percent reduction in monthly focal seizure frequency was 52.8% in the XEN1101 25 mg group, 46.4% in the XEN1101 20 mg group, and 33.2% in the XEN1101 10 mg group compared to 18.2% in the placebo group. Statistical significance was achieved for all dose groups compared to placebo with 2-sided p-values of p<0.001 for 25 mg vs. placebo, p<0.001 for 20 mg vs. placebo, and p=0.035 for 10 mg vs. placebo.

- A key secondary endpoint of the study was a responder analysis, which compared the proportion of study subjects treated with XEN1101 who achieved a ≥50% reduction in monthly focal seizures versus placebo. The percentage of subjects who achieved a >50% reduction in monthly focal seizures was 54.5% in the XEN1101 25 mg group, 43.1% in the XEN1101 20 mg group, and 28.3% in the XEN1101 10 mg group compared to 14.9% in the placebo group. Statistical significance was achieved for all dose groups compared to placebo with 2-sided p-values of p<0.001 for 25 mg vs. placebo, p<0.001 for 20 mg vs. placebo, and p=0.037 for 10 mg vs placebo.

- These marked reductions in seizures were associated with statistically significant improvements in overall status, as assessed by physicians using the Clinical Global Impression of Change (CGI-C) and by subject self-reporting using the Patient Global Impression of Change (PGI-C) scales in the XEN1101 25 mg group, which are shown in the table below with 2-sided p-values:

	XEN1101 25 mg (N=112)	**Placebo (N=114)**
CGI-C (Portion of Patients Much Improved or Very Much Improved)	46.4% (p<0.001)	22.8%
PGI-C (Portion of Patients Much Improved or Very Much Improved)	42.9% (p=0.001)	21.9%

In addition to the statistically significant CGI-C and PGI-C in the XEN1101 25 mg group, the XEN1101 20 mg group was statistically significant in PGI-C, while the XEN1101 20 mg group in CGI-C and the XEN1101 10 mg group for both CGI-C and PGI-C showed numerical improvements over placebo but were not statistically significant.

Key Safety and Tolerability Findings

- XEN1101 was generally well-tolerated in this study with adverse events (AEs) consistent with other ASMs. The incidence of treatment-emergent adverse events (TEAEs) was higher in the treatment groups as compared to the placebo group, with 62.3% of patients in the placebo group, 67.4% of patients in the XEN1101 10 mg group, 68.6% of patients in the XEN1101 20 mg group, and 85.1% of patients in the XEN1101 25 mg group experiencing at least one TEAE. The most common TEAEs across all XEN1101 dose groups (n=211) were dizziness (n=52, 24.6%), somnolence (n=33, 15.6%), fatigue (n=23, 10.9%), and headache (n=21, 10.0%). Two TEAEs of urinary retention were reported in the active treatment groups, one of which required a dose reduction, and both subjects remained on drug with no other changes or intervention. Electrocardiogram (ECG) interval changes were infrequent and evenly balanced between placebo and active treatment groups. There have been no TEAEs of pigmentary abnormalities reported during the double-blind phase of the study or in preliminary analysis during the ongoing open-label extension to date with approximately 70 subjects now treated more than 12 months.

- The incidence of treatment-emergent serious adverse events (SAEs) was similar in all four arms of the study with 2.6% of patients in the placebo group, 4.3% of patients in the XEN1101 10 mg group, 3.9% of patients in the XEN1101 20 mg group, and 2.6% of patients in the XEN1101 25 mg group experiencing at least one treatment-emergent SAE.

- There were 3.5% of subjects in the placebo group, 2.2% of subjects in the XEN1101 10 mg group, 13.7% of subjects in the XEN1101 20 mg group, and 15.8% of subjects in the XEN1101 25 mg group that had an AE leading to treatment discontinuation.

Mr. Ian Mortimer, Xenon's President and Chief Executive Officer stated, "We believe that the X-TOLE topline data support a very attractive clinical profile for XEN1101 with desirable attributes that help differentiate it from other ASMs and suggest XEN1101

could be highly competitive in the future adult focal seizure market. Of importance, the XEN1101 efficacy data are especially compelling given that approximately 50% of the subjects in X-TOLE were using three concomitant ASMs, suggesting that this was potentially an even more challenging patient population than previous studies with other ASMs. Additionally, these data signal activity of XEN1101 in the central nervous system, which further supports our plans to develop XEN1101 in other indications, including major depressive disorder and other types of epilepsy."

Xenon intends to gather input from the U.S. Food and Drug Administration and other regulatory agencies to continue planning the future clinical development of XEN1101. In addition, the X-TOLE open-label extension, which has been expanded to three years, is expected to generate important long-term data for XEN1101.

Conference Call Information
Xenon will host a conference call and live webcast with slides today at 7:30 am Eastern Time (4:30 am Pacific Time) to discuss the topline results from the XEN1101 Phase 2b X-TOLE clinical trial. The webcast will be broadcast live on the Investors section of the Xenon website. To participate in the call, please dial (855) 779-9075, or (631) 485-4866 for international callers, and provide conference ID number 4481713.

About Xenon Pharmaceuticals Inc.

We are a clinical stage biopharmaceutical company committed to developing innovative therapeutics to improve the lives of patients with neurological disorders. We are advancing a novel product pipeline of neurology therapies to address areas of high unmet medical need, with a focus on epilepsy. For more information, please visit www.xenon-pharma.com.

Safe Harbor Statement
This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995 and Canadian securities laws. These forward-looking statements are not based on historical fact, and include statements regarding the potential efficacy, safety profile, future development plans, addressable market, regulatory success and commercial potential of XEN1101; the anticipated initiation of future clinical trials for XEN1101; the timing and results of our planned interactions with regulators regarding XEN1101; and our ability to successfully develop and obtain regulatory approval of XEN1101. These forward-looking statements are based on current assumptions that involve risks, uncertainties and other factors that may cause the actual results, events or developments to be materially different from those expressed or implied by such forward-looking statements. These risks and uncertainties, many of which are beyond our control, include, but are not limited to: the impact of the COVID-19 pandemic on our business, research and clinical development plans and timelines and results of operations, including impact on our clinical trial sites, collaborators, and contractors who act for or on our behalf, may be more severe and more prolonged than currently anticipated; clinical trials may not demonstrate safety and efficacy of any of our or our collaborators' product candidates; promising results from pre-clinical development activities or early clinical trial results may not be replicated in later clinical trials; our assumptions regarding our planned expenditures and sufficiency of our cash to fund operations may be incorrect; any of our or our collaborators' product candidates, including XEN1101, may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; we may not achieve additional milestones in our proprietary or partnered programs; regulatory agencies may impose additional requirements or delay the initiation of clinical trials; regulatory agencies may be delayed in reviewing, commenting on or approving any of our or our collaborators' clinical development plans as a result of the COVID-19 pandemic, which could further delay development timelines; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; impact of new or changing laws and regulations; adverse conditions in the general domestic and global economic markets; as well as the other risks identified in our filings with the Securities and Exchange Commission and the securities commissions in British Columbia, Alberta and Ontario. These forward-looking statements speak only as of the date hereof and we assume no obligation to update these forward-looking statements, and readers are cautioned not to place undue reliance on such forward-looking statements.

Media/Investors Contact:
Maria McClean / Jodi Regts
Xenon Pharmaceuticals Inc.
Phone: 604.484.3353 / 469-743-1834
Email: investors@xenon-pharma.com

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Source: Xenon Pharmaceuticals Inc.