Xenon Pharmaceuticals Presents Additional Positive Data from Phase 2b 'X-TOLE' Clinical Trial at the Annual Meeting of the American Epilepsy Society (AES 2021)

December 3, 2021

Topline Data Showed 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

Results from New Sub-Analyses Consistent with Positive Topline Data and Demonstrate Strong Efficacy Across Responder Subgroups and Increased Efficacy in Patients with Less Severe Disease

Xenon to Host Conference Call Today at 9:00 am Eastern Time

BURNABY, British Columbia, Dec. 03, 2021 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq:XENE), a neurology-focused biopharmaceutical company, today announced that additional positive data from new sub-analyses of the Phase 2b X-TOLE clinical trial will be presented in a scientific poster entitled "Phase 2b Efficacy and Safety of XEN1101, a Novel Potassium Channel Modulator, In Adults With Focal Epilepsy (X-TOLE)" and at a Xenon-sponsored scientific symposium at the Annual Meeting of the American Epilepsy Society (AES 2021).

On October 4, 2021, Xenon announced that the X-TOLE trial had 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). Primary and secondary measures in the topline data set 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.

In addition to the topline data, additional sub-analyses have been completed and are being presented at AES 2021. These new analyses include the proportion of patients with at least a 75% reduction in monthly focal seizure frequency from baseline along with the proportion of patients who achieved 100% reduction in monthly seizure frequency from baseline. Efficacy results are summarized in the following table; all p-values are 2-sided comparing the active dose to placebo for the pre-specified primary and secondary seizure reduction endpoints:

	XEN1101 25 mg (N=112)	**XEN1101 20 mg (N=51)**	**XEN1101 10 mg (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%
Patients with **at least a 75%** reduction in monthly focal seizure frequency from baseline	29.5%	29.4%	8.7%	6.1%
Patients with **100%** reduction in monthly focal seizure frequency from baseline	6.3%	7.8%	2.2%	1.8%

Additional sub-analyses were performed in patients with different baseline characteristics given that X-TOLE included a "difficult-to-treat" patient population as defined by the number of prior failed anti-seizure medications (ASMs), concomitant ASMs on study, and baseline seizure burden. The table below outlines a sub-group analyses of median percent reduction in seizures within the 25 mg dose group, showing that there was a significant increase in seizure reduction in patients with less disease severity at baseline:

	XEN1101 25 mg Median reduction from baseline in monthly focal seizures frequency
Overall in X-TOLE (N=112)	52.8%

Prior failed ASMs > 6	43.0%
Prior failed ASMs < 6	58.0%
Concomitant ASMs = 3	50.8%
Concomitant ASMs ≤ 2	60.9%
Baseline seizures > 8.5 per month	50.8%
Baseline seizures ≤ 8.5 per month	70.6%

Dr. Christopher Kenney, Xenon's Chief Medical Officer commented, "We are excited to present detailed clinical data from our XEN1101 X-TOLE Phase 2b clinical trial at AES 2021. Importantly, data from additional analyses of sub-groups in the X-TOLE study are consistent with the topline data set, which demonstrated strong evidence supporting the efficacy, safety, and tolerability of XEN1101. Upon review of the scientific literature, we believe that the X-TOLE demographics represent one of the most severe patient populations studied in an adult focal epilepsy clinical trial to date, as measured by the number of seizures at baseline, the number of prior failed ASMs prior to study initiation, and the number of concomitant ASMs. In the context of this 'difficult-to-treat' population, XEN1101 demonstrated impressive efficacy. More than half of the patients in the 25 mg dose group experienced at least a 50% reduction in monthly focal seizure frequency from baseline, and, further, more than 50% of those patients experienced a 75% or greater reduction in monthly focal seizure frequency from baseline. In those patients with less severe seizure burden at baseline (less than or equal to 8.5 seizures per month), we saw seizure freedom rates of 17.6% and 13.8% in the 20 mg and 25 mg dose groups, respectively. Based on these X-TOLE results, we believe XEN1101 has a highly competitive and differentiated clinical profile when compared to other ASMs and could play an important role in treating focal epilepsy."

Highlights of X-TOLE Efficacy Results:

- 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.

- 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 pre-specified 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%

The XEN1101 25 mg group was statistically significant in CGI-C and PGI-C, and 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.

- In addition to the pre-specified primary and secondary analyses, other exploratory and sub-group analyses have been completed that show increased seizure reduction in those patients with less disease severity as measured by the number of prior failed ASMs, number of concomitant ASMs on study, and baseline seizure burden. In addition, an analysis of seizure reduction across seizure subtypes showed a median percent reduction in monthly focal seizure frequency of 86.9% in 'type 4' focal seizures that lead to generalized tonic-clonic seizures in the 25 mg dose group. A time-to-event analysis analyzing the time to reach the baseline monthly focal seizure count during the double-blind period showed a marked dose-dependent decrease in the rate of seizure recurrence when comparing XEN1101 to placebo.

Highlights of X-TOLE Safety Results:

- 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.

- TEAEs greater than or equal to 5% in all treatment arms were attributed to nervous system disorders; psychiatric disorders; general disorders; gastrointestinal disorders; eye disorders; and infections, with the majority related to the central nervous system, mild or moderate in severity and occurring early in the treatment period. Across all XEN1101 dose groups (n=211), the most common TEAEs were dizziness (n=52, 24.6%), somnolence (n=33, 15.6%), fatigue (n=23, 10.9%), and headache (n=21, 10.0%). The breakdown of subjects with dizziness across dose groups including placebo is as follows: 8 subjects (7.0%) in the placebo group, 3 subjects (6.5%) in the 10 mg group, 13 subjects (25.5%) in the 20 mg group, and 36 subjects (31.6%) in the 25 mg group.

- 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.

- 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. There was no evidence of urinary retention based upon mean differences across treatment groups in the total or individual items of the American Urological Associations Symptoms Index.

- There was no cardiovascular signal of concern based on vital signs from resting or orthostatic tests; there were no safety signals of concern from physical or neurologic exams; and there were no signals of concern from ECGs, safety labs or urinalysis.

- Weight changes were modest with mean changes of 0.2 kg in the placebo group, 0.6 kg in the 10 mg group, 1.6 kg in the 20 mg group and 1.9 kg in the 25 mg group.

- 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 80 subjects now treated more than 12 months.

Mr. Ian Mortimer, Xenon's President and Chief Executive Officer stated, "We believe the X-TOLE data package provides compelling evidence of XEN1101's activity in the CNS, and our team is focused on finalizing the clinical development plans for XEN1101, including a Phase 3 program in adult focal epilepsy and potentially other epilepsy indications. We expect to conduct a planned, end-of-Phase 2 meeting with the FDA in the second quarter of 2022, followed by the initiation of our Phase 3 adult focal epilepsy program anticipated in the second half of 2022. 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. We are also advancing the clinical development of XEN1101 in major depressive disorder through an investigator-led Phase 2 proof-of-concept study with collaborators at Mount Sinai and intend to initiate a company-sponsored MDD clinical trial in the first half of 2022."

About the Phase 2b X-TOLE Clinical Trial

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.

Conference Call Information

Xenon will host a conference call and live audio webcast today at 9:00 am Eastern Time (6:00 am Pacific Time) to discuss the X-TOLE results presented at AES 2021. 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 8639677.

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.

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