Xenon Announces Positive Phase 1 and New Preclinical Data at IASP 2026 Supporting Advancement of XEN1701 and XEN1120 to Phase 2 Proof-of-Concept Studies in Acute Pain

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- *XEN1701 achieved target profile, including desired $Na_V1.7$ receptor occupancy in both the peripheral and central nervous system, and was generally well-tolerated with no notable autonomic cardiovascular effects*
- *XEN1120 achieved plasma levels predictive of analgesic effects based on preclinical modeling and was generally well-tolerated*
- *New preclinical data in cynomolgus monkeys demonstrated significant reductions in capsaicin-evoked heat pain for $Na_V1.7$ and K_V7 compounds*
- *Phase 2 proof-of-concept studies assessing XEN1701 and XEN1120 in acute pain expected to initiate in H1 2027*

VANCOUVER, BC and BOSTON, MA, Oct. 29, 2026 (GLOBE NEWSWIRE) -- Xenon Pharmaceuticals Inc. (Nasdaq: XENE), a neuroscience-focused biopharmaceutical company dedicated to drug discovery, clinical development, and commercialization of life-changing therapeutics for patients in need, today announced positive Phase 1 study results and new preclinical data supporting the advancement of XEN1701 and XEN1120 to Phase 2 proof-of-concept studies in acute pain. Data were presented in two poster presentations during the International Association for the Study of Pain (IASP) 2026 World Congress on Pain, taking place October 26–30, 2026 in Bangkok, Thailand.

XEN1701 and XEN1120 are potent, selective ion channel modulators designed to target $Na_V1.7$ and K_V7, respectively. $Na_V1.7$ and K_V7 represent novel, non-opioid pain targets with significant supportive preclinical, clinical, and human genetic and expression data. XEN1701 and XEN1120 have been developed using Xenon's deep expertise in genetics, ion channel biology, and novel chemistries to enable potent, selective ion channel targeting.

"This is an incredibly exciting milestone for Xenon given our significant history with both $Na_V1.7$ and K_V7, and it brings us closer to delivering a new generation of innovative non-opioid therapeutics for acute and chronic pain," said Ian Mortimer, President and CEO of Xenon. "The XEN1701 data are especially exciting as $Na_V1.7$ has long been recognized by the field as having the strongest genetic evidence among novel pain targets, and many companies have tried to develop $Na_V1.7$ inhibitors without success. The Phase 1 data strengthen our belief that XEN1701 has a profile unlike any $Na_V1.7$ compound previously tested in the clinic, achieving high target receptor occupancy without a notable pattern of cardiovascular effects. We are optimistic that we may be on the precipice of realizing the potential of this promising pain target."

"Our Phase 1 studies of XEN1701 and XEN1120 achieved all of our goals, demonstrating the desired profiles for both compounds and strongly supporting their advancement to Phase 2 acute pain studies for rapid proof-of-concept," said Chris Kenney, MD, Chief Medical Officer of Xenon. "We also are highly encouraged by additional preclinical data shared in these posters, including data in cynomolgus monkeys where a Xenon $Na_V1.7$ inhibitor comparable to XEN1701 demonstrated up to a 100% reduction in evoked pain when central and peripheral receptor occupancies were above 75%, without effects on blood pressure or heart rate in this preclinical model. In the same model, a K_V7 compound comparable to XEN1120 also demonstrated a significant reduction in evoked pain, and XEN1120 has also demonstrated analgesic activity in the mouse formalin model during the acute phase, which has typically only been seen with opioids."

Xenon is finalizing Phase 2 acute pain study designs for each program and expects to initiate both studies in the first half of 2027.

Highlights from XEN1701 Poster: "XEN1701, a Phase 2-Ready $Na_V1.7$ Inhibitor: Advancing a Novel Non-Opioid Strategy for Pain"

- **Study Design:** Healthy participants were enrolled in Single Ascending Dose (SAD), Multiple Ascending Dose (MAD), food-effect, and cerebrospinal fluid (CSF) collection cohorts (n=76 XEN1701 and n=22 placebo) to assess the safety, tolerability, pharmacokinetics (PK), food effect, and central nervous system (CNS) penetration of XEN1701. CSF sampling was performed in open-label cohorts to measure CNS drug exposure.
- **Free Drug Exposure:** XEN1701 exhibited dose-dependent and rapid increases in plasma exposure across the evaluated dose ranges. XEN1701 and its active metabolite demonstrated a consistent metabolite-to-parent exposure ratio across all doses and the combined exposure profile supports the potential to achieve therapeutically relevant $Na_V1.7$ inhibition.
- **High Receptor Occupancy:** Plasma and CSF sampling and predicted receptor occupancy modeling indicated that the proposed Phase 2 dose levels achieved and maintained more than 75% $Na_V1.7$ receptor occupancy in both the peripheral and central nervous system with twice-daily (BID) dosing. Human genetic evidence has established that more than 75% $Na_V1.7$ inhibition is associated with a pain-free clinical phenotype.

- **Generally Well-Tolerated Safety Profile:** There were no treatment-related, dose-limiting treatment-emergent adverse events (TEAEs), serious TEAEs, or TEAEs leading to study drug discontinuation. Most TEAEs were mild; those observed in more than one participant in the MAD cohorts included headache (10% XEN1701 overall vs. 10% pooled placebo), dizziness (6.7% vs. 10% placebo), and postural dizziness (6.7% vs. 0% placebo).
    - Treatment-related TEAEs potentially related to autonomic cardiovascular effects were infrequent and balanced (6.6% vs. 4.2% placebo), with no consistent dose- or exposure-related patterns and none occurring at the highest dose levels. These findings support that the proposed Phase 2 dose levels have not shown a consistent pattern of autonomic cardiovascular effects of the kind reported for other $Na_V1.7$ compounds in published literature.
- **Significant Pain Reduction Observed in Non-Human Primates:** Preclinical data evaluating XPC-4, a Xenon compound comparable to XEN1701, in cynomolgus monkeys demonstrated that doses achieving more than 75% $Na_V1.7$ receptor occupancy were associated with significant reductions in capsaicin-evoked heat pain, including ~85-100% reduction at the two highest doses tested. No clinically meaningful change in systolic arterial blood pressure or heart rate relative to vehicle was observed with XPC-4 at the highest two doses tested.

Highlights from XEN1120 Poster: "XEN1120, a Phase 2-Ready K_V7 Channel Opener: Advancing a Novel Non-Opioid Strategy for Pain"

- **Study Design:** Healthy participants were enrolled in SAD, MAD, and food-effect cohorts (n=54 XEN1120 and n=18 placebo) to assess the safety, tolerability, PK, and food effect of XEN1120.
- **Plasma Levels in Predicted Efficacious Range:** Clinical PK data demonstrated that XEN1120 exceeded the predicted efficacious exposures established from preclinical rodent and non-human primate efficacy models. PK modeling demonstrated that a loading dose rapidly achieved target exposures while maintenance dosing sustained plasma concentrations within the predicted efficacious range for the duration required for an acute pain proof-of-concept study.
- **Generally Well-Tolerated Safety Profile:** There were no treatment-related, dose-limiting TEAEs, serious or severe TEAEs, or TEAEs leading to study drug discontinuation. Most TEAEs were mild and the most common TEAEs observed in more than one participant in the MAD cohorts included tachycardia (33.2% XEN1120 overall vs. 12.5% pooled placebo), dizziness (29.2% vs. 0% placebo) and somnolence (25% vs. 0% placebo).
- **Robust Analgesic Activity in Mouse Formalin Model:** The mouse formalin model involves a biphasic pain response consisting of an acute nociceptive phase, followed by a longer lasting inflammatory phase. Many analgesics work in the inflammatory phase, whereas only opioids typically show efficacy in the acute phase. XEN1120 demonstrated dose-dependent pain reductions in the acute phase of the formalin model, and notably, at exposures that were substantially lower than the comparator flupirtine, an earlier generation pain treatment with a mechanism of action involving potassium channel opening.
- **Significant Pain Reduction Observed in Non-Human Primates:** Preclinical data evaluating XPC-B, a Xenon compound comparable to XEN1120, demonstrated dose-dependent reductions in capsaicin-evoked heat pain in cynomolgus monkeys. Analgesic activity was achieved at approximately 2.3-fold lower exposures relative to the formalin mouse model, suggesting the potential to achieve analgesic activity at lower doses in humans.

Acute and chronic pain affects more people than diabetes, heart disease, and cancer combined, yet effective, long-term treatment options are scarce. Acute pain serves as the body's normal, short-term alarm signal in response to an injury or illness. In contrast, chronic pain is a widespread condition defined by IASP as pain that lasts or recurs for more than three months, and may persist even after the initial cause has healed. It's more common than many realize; 2021 data from the U.S. Centers for Disease Control and Prevention (CDC) show that it affects more than one in five American adults, often impacting daily life and well-being.

About Xenon's Pain Pipeline

Xenon's clinical-stage pain pipeline includes three investigational therapeutic programs, including XEN1701 and XEN1720, which are designed to block the activity of the sodium channels ($Na_V1.7$) that trigger pain signaling, and XEN1120, which is designed to enhance the activity of the potassium channels (K_V7) that mitigate pain signals.

Xenon has extensive history researching $Na_V1.7$ as a novel pain target. This history started more than 20 years ago with the identification of a loss of function in SCN9A, which encodes the $Na_V1.7$ sodium channel, as the cause of congenital indifference to pain (CIP), an extremely rare autosomal recessive disorder whose carriers are unable to feel pain but are otherwise healthy. More recently, Xenon has focused on optimizing chemistry to address the limitations of earlier drug candidates targeting $Na_V1.7$, resulting in its current clinical candidates XEN1701 and XEN1720.

XEN1120 reflects more than a decade of Xenon's research on K $_V7$ channels. Multiple lines of evidence support K_V7 as a therapeutic target for pain. K_V7 channels are broadly expressed throughout the peripheral and central pain pathways. They play a significant role in the initial transduction of pain stimuli into pain signals, the transmission of those pain signals along nociceptive neurons, and the relay from peripheral sensory neurons to spinal cord neurons in the central nervous system. Dysfunction or downregulation of K_V7 channel activity has also been observed in altered pain states, contributing to sensory neuron hyperexcitability and enhanced pain signaling.

About Xenon Pharmaceuticals Inc.

Xenon Pharmaceuticals (Nasdaq: XENE) is a neuroscience-focused biopharmaceutical company dedicated to drug discovery, clinical development, and commercialization of life-changing therapeutics for patients in need. Xenon's lead molecule, azetukalner, is a novel, potent K_V7 potassium channel opener in late-stage clinical development for the treatment of epilepsy, major depressive

disorder and bipolar depression. Xenon is also advancing an early-stage portfolio of multiple promising potassium and sodium channel modulators, including K_V7 and $Na_V1.7$ programs in Phase 1 development for the potential treatment of pain. Xenon has offices in Vancouver, British Columbia, and Boston, Massachusetts. For more information, visit www.xenon-pharma.com and follow us on LinkedIn and X.

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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 status of, and potential results from, pre-clinical and clinical studies; the potential efficacy, safety profile, future development plans in current and anticipated indications, addressable market, regulatory success and commercial potential of our and our partners' product candidates; the efficacy of our clinical study designs; our ability to achieve milestones in our pipeline and development programs, including the initiation of clinical studies; and our ability to successfully develop, obtain regulatory approval for, and commercialize our product candidates. 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: clinical studies 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 study results may not be replicated in later clinical studies; our assumptions regarding our planned expenditures and sufficiency of our cash to fund operations may be incorrect; our ongoing discovery and pre-clinical efforts may not yield additional product candidates; any of our or our collaborators' product candidates 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 delay the initiation or completion of clinical studies or impose additional requirements prior to approval; the impact of market, industry, and regulatory conditions on clinical study enrollment; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; the impact of new or changing laws and regulations; the impact of unstable economic conditions in the general domestic and global economic markets; adverse conditions from geopolitical events; as well as the other risks identified in our filings with the U.S. 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.

Contacts

For Investors:
Laura Perry/Emily Huang
Argot Partners
Xenon@argotpartners.com

For Media:
Colleen Alabiso
Senior Vice President, Corporate Affairs
media@xenon-pharma.com