Ultragenyx Announces First Patient Dosed in Pivotal Phase 3 Aspire Study Evaluating GTX-102 in Angelman Syndrome

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Company on track to initiate the Aurora study to evaluate GTX-102 in other Angelman syndrome genotypes and in other age groups in 2025

NOVATO, Calif., Dec. 19, 2024 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), today announced that the first patient has been dosed in the pivotal Phase 3 *Aspire* study (NCT06617429) evaluating the efficacy and safety of GTX-102, its investigational antisense oligonucleotide (ASO) for Angelman syndrome.

"Initiation of patient dosing in our Phase 3 *Aspire* study represents an important step forward in the development of an effective, and much needed, treatment for patients and families affected by Angelman syndrome," said Eric Crombez, M.D., chief medical officer at Ultragenyx. "Our goal with *Aspire* is to confirm the safety and clinical efficacy of GTX-102 in a large, randomized trial with a population that represents the majority of patients with Angelman syndrome. Additionally, the *Aurora* study will further assess safety and validate efficacy in patients with different genotypes and in younger and older patients."

The global Phase 3 *Aspire* study will enroll approximately 120 children ages 4 to 17 with Angelman syndrome with a genetically confirmed diagnosis of full maternal *UBE3A* gene deletion. Participants will be randomized 1:1 to receive GTX-102 by intrathecal injection via lumbar puncture or to the sham comparator group during the 48-week primary efficacy analysis period. Participants in the active treatment group will receive three, monthly 8 mg loading doses of GTX-102 followed by dosing in a maintenance period that will increase to a maximum dose of 14 mg of GTX-102 quarterly. Patients in the sham comparator group will be eligible to crossover onto treatment after Week 48 is complete. The primary endpoint will be improvement in cognition assessed by Bayley-4 cognitive raw score, and the key secondary endpoint will be the Multi-domain Responder Index (MDRI) across the five domains of cognition, receptive communication, behavior, gross motor function, and sleep.

"Angelman syndrome affects cognitive and motor function, making walking, communicating, and performing many everyday tasks more difficult for individuals living with Angelman syndrome. As a united community, ASF and FAST work together to further awareness and treatment of Angelman syndrome and are excited by all the recent progress in research and drug development. The initiation of the Phase 3 *Aspire* study by Ultragenyx is a significant achievement and something the community should celebrate," stated Amanda Moore, chief executive officer at the Angelman Syndrome Foundation (ASF) and Ryan Fischer, chief operating officer at Foundation for Angelman Syndrome Therapeutics (FAST), in a joint statement.

At the 2024 Foundation for Angelman Syndrome Therapeutics (FAST) Global Science Summit in November, the company presented data from the Phase 1/2 study that confirmed the Phase 3 *Aspire* study dosing strategy and that the study is amply powered to establish the efficacy of GTX-102 on the primary endpoint of change in cognition, as measured by Bayley-4, or the key secondary endpoint of MDRI at the Week 48 timepoint.

U.S. residents can learn more by visiting www.ultraclinicaltrials.com.

About GTX-102
GTX-102 is an investigational antisense oligonucleotide (ASO) therapy delivered via intrathecal administration and designed to target and inhibit expression of the *UBE3A antisense transcript (UBE3A-AS)* to prevent silencing of the paternally inherited allele of the *UBE3A* gene and reactivate expression of the deficient protein. GTX-102 has been granted Orphan Drug Designation, Rare Pediatric Disease Designation, and Fast Track Designation from the FDA and Orphan Designation and PRIME designation from the EMA.

About Angelman Syndrome
Angelman syndrome is a rare, neurogenetic disorder caused by loss-of-function of the maternally inherited allele of the *UBE3A* gene. The maternal-specific inheritance pattern of Angelman syndrome is due to genomic imprinting of *UBE3A* in neurons of the central nervous system (CNS), a naturally occurring phenomenon in which the maternal *UBE3A* allele is expressed and the paternal *UBE3A* is not. Silencing of the paternal *UBE3A* allele is regulated by the *UBE3A-AS*, the intended target of GTX-102. In almost all cases of Angelman syndrome, the maternal *UBE3A* allele is either missing or mutated, resulting in limited to no protein expression. This condition is generally not inherited but instead occurs spontaneously. It is estimated to affect approximately 60,000 people in commercially accessible geographies.

Angelman syndrome is a lifelong neurodevelopmental disorder that causes cognitive impairment, motor impairment, balance issues and debilitating seizures. Some individuals with Angelman syndrome are unable to walk and most do not speak. Anxiety and disturbed sleep can be serious challenges in individuals with Angelman syndrome. Although individuals with Angelman syndrome have a normal lifespan, they require continuous care and are unable to live independently. Angelman syndrome is not a degenerative disorder, but the loss of the *UBE3A* protein expression in neurons results in abnormal communications between neurons. Angelman syndrome is often misdiagnosed as autism or cerebral palsy. There are no currently approved therapies for Angelman syndrome; however, several symptoms of this disorder can be reversed in adult animal models of Angelman syndrome, suggesting that improvement of symptoms can potentially be achieved at any age.

About Ultragenyx
Ultragenyx is a biopharmaceutical company committed to bringing novel therapies to patients for the treatment of serious rare and ultrarare genetic diseases. The company has built a diverse portfolio of approved medicines and treatment candidates aimed at addressing diseases with high unmet medical need and clear biology, for which there are typically no approved therapies treating the underlying disease.

The company is led by a management team experienced in the development and commercialization of rare disease therapeutics. Ultragenyx's strategy is predicated upon time- and cost-efficient drug development, with the goal of delivering safe and effective therapies to patients with the utmost urgency.

For more information on Ultragenyx, please visit the company's website at: www.ultragenyx.com.

Forward-Looking Statements and Use of Digital Media
Except for the historical information contained herein, the matters set forth in this press release, including statements related to Ultragenyx's

expectations and projections regarding its future operating results and financial performance, business plans and objectives for GTX-102, expectations regarding the tolerability and safety of GTX-102, and future clinical and regulatory developments for GTX-102 are forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements involve substantial risks and uncertainties that could cause our clinical development programs, collaboration with third parties, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainty of clinical drug development and unpredictability and lengthy process for obtaining regulatory approvals, the ability of the company to successfully develop GTX-102, the company's ability to achieve its projected development goals in its expected timeframes, the risk that results from earlier studies may not be predictive of future study results, risks related to adverse side effects, risks related to reliance on third party partners to conduct certain activities on the company's behalf, smaller than anticipated market opportunities for the company's products and product candidates, manufacturing risks, competition from other therapies or products, and other matters that could affect sufficiency of existing cash, cash equivalents and short-term investments to fund operations, the company's future operating results and financial performance, the timing of clinical trial activities and reporting results from same, and the availability or commercial potential of Ultragenyx's products and drug candidates. Ultragenyx undertakes no obligation to update or revise any forward-looking statements.

For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of Ultragenyx in general, see Ultragenyx's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 6, 2024, and its subsequent periodic reports filed with the SEC.

In addition to its SEC filings, press releases and public conference calls, Ultragenyx uses its investor relations website and social media outlets to publish important information about the company, including information that may be deemed material to investors, and to comply with its disclosure obligations under Regulation FD. Financial and other information about Ultragenyx is routinely posted and is accessible on Ultragenyx's Investor Relations website (https://ir.ultragenyx.com/) and LinkedIn website (https://www.linkedin.com/company/ultragenyx-pharmaceutical-inc-/).

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