Ultragenyx Receives FDA Agreement to Expand Ongoing Global Phase 1/2 Trial Evaluating GTX-102 in Patients with Angelman Syndrome in the U.S.

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Amended U.S. protocol increases loading and maintenance doses to similar range as ex-U.S. expansion cohorts

NOVATO, Calif., May 17, 2023 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced that the U.S. Food and Drug Administration (FDA) has reviewed and agreed to a protocol amendment to the Phase 1/2 study of GTX-102 in pediatric patients with Angelman syndrome that enables the company to harmonize dose ranges in the U.S. with those being used in ex-U.S. cohorts of the study. Outside of the U.S., the Phase 1/2 study has been actively enrolling and dosing patients in the expansion cohorts to verify the GTX-102 dose and treatment regimen that will be used in the Phase 3 program.

“Agreement on the protocol amendment enables comparable dose ranges across all geographies and allows us to move forward rapidly to complete the study. We have begun working urgently to activate multiple study sites in the U.S. and plan to begin enrollment as quickly as possible,” said Scott Stromatt, M.D., SVP and chief medical officer of neurology clinical development at Ultragenyx. “We are eager to expand the study in the U.S. to build on the encouraging data, which demonstrate important clinical activity across multiple functional domains impacted by Angelman syndrome with an acceptable safety profile.”

About the Phase 1/2 study

The Phase 1/2, open-label, dose-escalating study is evaluating the safety and tolerability of GTX-102 in pediatric patients with Angelman syndrome with a genetically confirmed diagnosis of full maternal *UBE3A* gene deletion. The study is also looking at clinical response as measured by a panel of efficacy assessments for the functional domains impacted in Angelman syndrome. Patients in the earlier dose-escalation cohorts of the study have moved into long-term maintenance dosing, and the study is now enrolling the new expansion cohorts to verify the GTX-102 dose range and treatment regimen that will be used in the Phase 3 program. As of May 4, 2023, 13 patients have had more than 12 months of exposure to GTX-102, with the longest more than 18 months.

The ex-U.S. portion of the study, which includes sites in Europe, Canada and Australia, is currently enrolling patients in expansion cohorts. As additional investigator sites open in the U.S., the study will begin enrolling expansion cohorts using similar dose ranges to the ex-U.S. study. The study will enroll approximately 40 patients across the expansion cohorts. U.S. patients that initiated the study on the 2 mg dose or in the comparator group will begin dosing under the amended protocol.

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* antisense transcript (*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 1 in 12,000 to 1 in 20,000 people globally.

Individuals with Angelman syndrome have developmental delay, balance issues, motor impairment, 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. While 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 GTX-102

GTX-102 is an investigational antisense oligonucleotide delivered via intrathecal administration and designed to target and inhibit expression of *UBE3A-AS*. Nonclinical studies show that GTX-102 reduces the levels of *UBE3A-AS* and reactivates expression of the paternal *UBE3A* allele in neurons of the CNS. Reactivation of paternal *UBE3A* expression in animal models of Angelman syndrome has been associated with improvements in some of the neurological symptoms associated with the condition. GTX-102 has been granted Orphan Drug Designation, Rare Pediatric Disease Designation, and Fast Track Designation from the FDA.

About Ultragenyx Pharmaceutical Inc.

Ultragenyx is a biopharmaceutical company committed to bringing novel products to patients for the treatment of serious rare and ultrarare genetic diseases. The company has built a diverse portfolio of approved therapies and product candidates aimed at addressing diseases with high unmet medical need and clear biology for treatment, 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 Company's ability to successfully develop GTX-102 at lower doses, including the resolution of adverse events that were seen at higher doses, whether lower doses of GTX-102 are sufficiently effective to support the continued development of the program, risks related to timing of and successful activation of clinical sites for the study of GTX-102, risks related to serious or undesirable side effects of GTX-102 and our other product candidates, the company's ability to achieve its projected development goals in its expected timeframes, 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 May 5, 2023, 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-/mycompany/).

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