Ultragenyx Announces Successful End-of-Phase 2 Meeting with FDA for GTX-102 Angelman Syndrome Program

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Alignment with FDA on Phase 3 study primary endpoint of Bayley-4 cognition and key secondary endpoint of Multi-Domain Responder Index (MDRI)

Phase 3 study on track to initiate by the end of this year

NOVATO, Calif., July 17, 2024 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced the successful completion of an end-of-Phase 2 (EoP2) meeting with the U.S. Food and Drug Administration (FDA), supporting its Phase 3 study plans for GTX-102, an antisense oligonucleotide for Angelman syndrome.

"FDA alignment on our Phase 3 study design for GTX-102 allows for rapid initiation of a global double-blind sham-controlled pivotal study by the end of this year," said Eric Crombez, M.D., chief medical officer at Ultragenyx. "In addition to this pivotal study in patients with a full *UBE3A* gene deletion, we are working to initiate a study to evaluate GTX-102 in patients with other mutations. This will allow for the potential treatment of more children and adults impacted by this devastating disease."

Phase 3 design and next steps
The EoP2 meeting focused on discussion of the Company's interim Phase 1/2 data and resulted in alignment with the FDA on the Phase 3 study design and endpoints. The pivotal Phase 3, will be a global, randomized, double-blind, sham-controlled trial and will include a 48-week primary efficacy analysis period enrolling approximately 120 patients with Angelman syndrome with a genetically confirmed diagnosis of full maternal *UBE3A* gene deletion. The primary endpoint will be improvement in cognition assessed by Bayley-4 cognitive raw score. Control patients completing the study will be eligible to roll over onto treatment after the double-blind period is over.

Previously disclosed results from the Phase 1/2 study showed that *UBE3A* gene deletion patients treated with GTX-102 experienced rapid, progressive and clinically significant improvement in cognition, as assessed by Bayley-4, that was far greater than the minimal change observed in Natural History data[1] in deletion patients. *UBE3A* gene deletion patients are at the severe end of the clinical spectrum, with lower Bayley scores at baseline, and demonstrate a much slower rate of skill attainment compared to, for example, *UBE3A* missense mutation patients, who demonstrate higher Bayley cognition improvement in Natural History data.[2] In the Phase 1/2 study, GTX-102 treated patients also demonstrated meaningful improvements in other domains of communication, motor function, sleep problems, and behavior.

The Phase 3 study will include the key secondary endpoint of the Multi-domain Responder Index (MDRI) across all five domains of cognition, receptive communication, behavior, gross motor function, and sleep. Individual secondary endpoints were also discussed and aligned on with the FDA for the domains of communication, behavior, motor function and sleep. Additional feedback on the conduct and analysis of these endpoints may be received from the FDA's Division of Clinical Outcomes Assessment.

Global regulatory progress
The company has also participated in a PRIME meeting with the European Medicines Agency, receiving acceptance of the overall Phase 3 study design, dosing and evaluations. The company expects to meet with Japan's Pharmaceuticals and Medical Devices Agency in the coming weeks to inform and discuss the Phase 3 study design.

Additional genotypes and ages to be studied in Phase 3
In addition to the randomized, controlled Phase 3 study, the company discussed with the FDA its plans to initiate an open-label clinical study to evaluate the safety and efficacy of GTX-102 for the treatment of patients with other Angelman syndrome genotypes and in other age groups. The goal of this additional study would be to enable treatment across a broad array of Angelman patient types.

U.S. residents can learn more about the Angelman syndrome program by visiting www.ultraclinicaltrials.com.

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 have shown that GTX-102 reduces levels of UBE3A-AS and reactivates expression of the paternal UBE3A allele in neurons of the central nervous system (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, 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 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 ~60,000 people in commercially accessible geographies.

Individuals with Angelman syndrome have a lifelong neurodevelopmental disorder including 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 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.

Ultragenyx 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 the clinical benefit, tolerability and safety of GTX-102 and the corresponding impact on patients, the anticipated dosing of the Phase 2 study for GTX-102 and the timing for initiation of a Phase 3 study for GTX-102 and associated regulatory meetings, 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 product 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 3, 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-/).

Contacts

Ultragenyx Pharmaceutical Inc.

Investors
Joshua Higa
+1-415-475-6370
ir@ultragenyx.com

Media
Carolyn Wang
+1-415-225-5050
media@ultragenyx.com

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[1] https://clinicaltrials.gov/study/NCT00296764

[2] https://pubmed.ncbi.nlm.nih.gov/33517526/