Ultragenyx Presents Positive Update on GTX-102 Angelman Syndrome Program at FAST's 17th Annual Global Science Summit

November 9, 2024

Phase 1/2 data show improvements across all domains and confirm that Phase 3 Aspire study is amply powered to establish efficacy of GTX-102

Phase 3 program on track to begin enrollment by end-of-year

NOVATO, Calif., Nov. 09, 2024 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced Phase 1/2 data in support of the Phase 3 *Aspire* study for GTX-102, its investigational antisense oligonucleotide for Angelman syndrome, that will be presented at the 2024 Foundation for Angelman Syndrome Therapeutics (FAST) Global Science Summit in Orlando, Florida.

"Cognition is the building block for the development and ascertainment of many new skills across a range of the domains we have evaluated in the Phase 1/2 study. The data presented at FAST reinforce that the *Aspire* Phase 3 primary endpoint of cognition, as measured by Bayley-4, appears very well powered to show statistically significant separation between the GTX-102 and sham arms," said Eric Crombez, M.D., chief medical officer at Ultragenyx. "We are on track to begin enrolling the Phase 3 *Aspire* study by the end of this year and have a robust and experienced global network of sites that will enable accelerated study execution."

The global Phase 3 *Aspire* study will enroll approximately 120 patients with Angelman syndrome with a genetically confirmed diagnosis of full maternal *UBE3A* gene deletion and will include a 48-week primary efficacy analysis period. 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.

As of the September Phase 1/2 data cut-off, patients in the Dose Expansion Cohorts demonstrated continued improvement across multiple domains at Week 48 (Day 338). Patients (n=40) in the Dose-escalation and Expansion Cohorts at Week 48 demonstrated a mean change in Bayley-4 Cognition Growth Scale Value (GSV) score from baseline of +6.7 compared to the minimally important difference of +5. Using the Phase 3 primary endpoint of Bayley-4 Cognition Raw score, the mean change from baseline was +10.9. This suggests the Phase 3 study has greater than 95% power to detect a treatment effect, even if the response in the sham arm is up to three times higher than observed changes in available natural history data[1].

Week 48 (Day 338) data from 28 patients in Expansion Cohorts A&B were evaluated with the Phase 3 key secondary endpoint of MDRI and showed a total net response of +2.0 (p-value < 0.0001). The data demonstrate that approximately 80% (22 of 28 patients) of patients have achieved clinically meaningful net improvement in at least one domain.

These data confirm that the Phase 3 *Aspire* study is amply powered to establish the efficacy of GTX-102 on the primary endpoint of cognition or the key secondary endpoint of MDRI at the Week 48 timepoint.

GTX-102 demonstrated a consistent and acceptable safety profile as of the data cutoff.

The latest Ultragenyx corporate deck with these data updates can be accessed at https://ir.ultragenyx.com/.

U.S. residents can learn more 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 the Phase 1/2 study
The Phase 1/2, open-label, multiple-dose, dose-escalating study is evaluating the safety and tolerability of GTX-102 administered by intrathecal (IT) injection to pediatric patients with Angelman syndrome with a genetically confirmed diagnosis of full maternal *UBE3A* gene deletion. The study is also assessing clinical response as measured by a panel of efficacy assessments for the functional domains impacted in Angelman syndrome. The study has enrolled and treated 74 patients in both Dose-escalation and Expansion Cohorts. Patients in Dose-escalation Cohorts 4-7 are receiving long-term maintenance dosing. Data from the Expansion Cohorts will be used to verify the GTX-102 dose and treatment regimen for the pivotal Phase 3 study.

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 approximately 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 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-/).

Contacts
Ultragenyx Pharmaceutical Inc.
Investors
Joshua Higa
+1-415-475-6370
ir@ultragenyx.com

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

---

1. *Linking Angelman and Dup15q Data for Expanded Research (LADDER)*