Ultragenyx Announces Data Demonstrating Treatment with UX111 Results in Significant Reduction in Heparan Sulfate Exposure in Cerebrospinal Fluid Correlated with Improved Long-term Cognitive Function in Patients with Sanfilippo Syndrome Type A (MPS IIIA)

February 6, 2024 1:00 PM EST

The latest data from the pivotal Transpher A and long-term follow-up studies will be presented at WORLDSymposium™ 2024

NOVATO, Calif., Feb. 06, 2024 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced data demonstrating treatment with UX111 (ABO-102) AAV gene therapy resulted in rapid and sustained decreased levels of heparan sulfate (HS) in cerebrospinal fluid (CSF) in patients with Sanfilippo syndrome type A (MPS IIIA), and that sustained reduction in CSF HS exposure over time was correlated with improved long-term cognitive development. These data are from the modified intention to treat group (mITT) in the pivotal *Transpher A* study (N=17). The results of this study along with the additional data from the long-term follow-up study for these subjects will be presented at the WORLD*Symposium*™2024 20th annual research meeting taking place February 4-9 in San Diego.

"It's impressive to see how our study patients treated with UX111 have maintained their communication skills despite being the age in which regression begins to occur," stated Mireia del Toro, M.D., coordinator of the Metabolic Unit, Pediatric Neurology Department, Hospital Universitari Vall d´Hebron, Barcelona. "Sustaining the ability to communicate also has a very relevant impact on improving behavioral problems and thus family daily life."

Following treatment with UX111 ($3x10^{13}$ vg/kg), levels of CSF-HS decreased within the first month post treatment in all patients. 8 of 17 patients in the mITT group who reached 24 months post-treatment achieved an overall mean percent reduction from baseline of 51% ($p < 0.0001$). An alternative way to assess CSF-HS is to look at the reduction in CSF HS exposure over time post-administration of UX111 using time-normalized area under curve (AUC). The 17 patients in the mITT group had a mean follow-up duration of 29 months (range = 11.3-60 months). There was a mean reduction in CSF HS exposure of 63% ($p<0.0001$) using time-normalized AUC. This type of analysis incorporates all post-baseline reductions in CSF-HS available at the time of data cut-off (August 2023) and allows for a robust quantification of the treatment effect of UX111 on reduction of toxic CSF HS exposure over time.

Cognitive function was measured using Bayley-III (BSITD-IIID) cognitive raw scores and an estimated yearly rate of change (EYC) was calculated to reflect a patient-specific rate of change in BSITD-III cognitive raw scores after UX111 treatment. At the time of the data cut-off, the individual EYC in cognitive raw scores showed a positive rate of change indicating either stability or gains from baseline in 16 of the 17 patients during the expected window of plateau into decline, defined as >30 months of age. There was a statistically significant correlation between the CSF HS exposure and the EYC in cognitive raw score, which was maintained with and without adjustment for age, resulting in a Spearman's Rank Order Correlation Coefficient of -0.64 ($p=0.0076$) and -0.72 ($p=0.0011$), respectively. Specifically, 15 of 17 patients had both a reduction in toxic CSF HS exposure and an improvement in cognitive function.

"It's important to look at the impact of CSF-HS as the brain's length of exposure to a toxic substrate rather than just one moment in time and if you correct the underlying biochemical disease at a molecular level, you provide the ability for neurons to survive and the brain to maintain and gain function over time," said Emil D. Kakkis, M.D., Ph.D., chief executive officer and president of Ultragenyx. "This recovery from exposure takes time, and while we'll see rapid reduction in exposure, we then need to follow up over the course of several years to see the developmental gains in these children."

The most frequently reported treatment-related adverse events to date were elevations in liver enzymes and the majority of these events were mild (Grade 1) or moderate (Grade 2) in severity. The only treatment-related adverse event ≥ Grade 3 reported to date was one event of increased alanine aminotransferase (ALT) that resolved, which is a known effect of AAV gene therapy.

The *Transpher A* study has enrolled and treated 28 patients across 3 dose Cohorts at 5 sites in 3 countries. The high dose Cohort 3 ($3x10^{13}$ vg/kg) consists of 22 patients, and 17 are in the mITT group. The mITT group is defined as patients who were either age 0-2 years old, or patients older than 2 years with a cognitive developmental quotient of 60 or above at time of enrollment. These patients received the highest dose of UX111. Subjects who completed the Transpher A study were invited to enroll into a long term follow study. As of the data cut-off, 15 of the 17 patients were at least 2.5 years of age and 6 of 17 were over five years of age. Mean duration of follow-up post-treatment was 29 months. Both trials are ongoing, and patients will continue to be followed for a minimum of 5 years following treatment with UX111.

About UX111

UX111 is a novel gene therapy in Phase 1/2 development for Sanfilippo syndrome type A (MPS IIIA), a rare fatal lysosomal storage disease with no approved treatment that primarily affects the central nervous system (CNS). UX111 is dosed in a one-time intravenous infusion using a self-complementary AAV9 vector to deliver a functional copy of the SGSH gene to cells of the CNS and peripheral organs. The therapy is designed to address the underlying SGSH enzyme deficiency responsible for abnormal accumulation of heparan sulfate, a glycosaminoglycan, in the brain and throughout the body that results in progressive cell damage and neurodevelopmental and physical decline. The UX111 program has received Regenerative Medicine Advanced Therapy, Fast Track, Rare Pediatric Disease, and Orphan Drug designations in the U.S., and PRIME and Orphan medicinal product designations in the EU.

About the *Transpher A* and Long-term Follow-up Studies

The *Transpher A* Study is an ongoing, two-year, open-label, dose-escalation, Phase 1/2/3 global clinical trial assessing UX111 for the treatment of patients with Sanfilippo syndrome type A (MPS IIIA). The current eligibility criteria focused on a modified target population and enrolled patients from birth to 2 years of age, or patients older than 2 years with a cognitive developmental quotient of 60 or above based on BSITD-III. These patients received the highest dose of 3×10^{13} vg/kg UX111 gene therapy delivered using AAV9 technology via a single-dose intravenous infusion. The study endpoints include heparan sulfate levels in CSF, neurodevelopmental outcomes, ganglioside levels in CSF, brain volumes as measured by MRI and

safety. Upon completion of the *Transpher A* study, subjects treated with UX111 were invited to enroll in a long-term follow-up study for continued monitoring of safety and efficacy. Further details can be referenced here: https://clinicaltrials.gov/ct2/show/NCT02716246

About Sanfilippo Syndrome Type A (MPS IIIA)

Sanfilippo syndrome type A (MPS IIIA) is a rare, fatal lysosomal storage disease with no approved treatment that primarily affects the CNS and is characterized by rapid neurodevelopmental and physical decline, with onset in early childhood. MPS IIIA has a global incidence of one in 100,000 with a median life expectancy of 15 years.

Children with MPS IIIA present with global developmental delay which eventually leads to progressive language and cognitive decline and behavioral abnormalities and early death. Other symptoms include sleep problems, frequent ear infections and liver/spleen enlargement. MPS IIIA is caused by biallelic pathogenic variants in the *SGSH* gene that lead to a deficiency in the sulfamidase (SGSH) enzyme responsible for breaking down heparan sulfate, a glycosaminoglycans, which accumulate in cells throughout the body resulting in rapid health decline associated with the disorder.

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 UX111, expectations regarding the tolerability and safety of UX111, and future clinical and regulatory developments for UX111 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 UX111, the company's ability to achieve its projected development goals in its expected timeframes, 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 3, 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-/).

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

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