Ultragenyx Announces New Data Demonstrating that Treatment with UX111 AAV Gene Therapy Significantly Improved Clinical Function Across Multiple Developmental Domains in Children with Sanfilippo Syndrome Type A (MPS IIIA) Correlated with Sustained Reductions in CSF-HS

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Modified intent-to-treat group demonstrated +22.7 point (p<0.0001) treatment effect in the mean Bayley-III cognitive raw score compared to natural history data (ages 24-60 months)

Older children with more advanced disease demonstrated retention of clinically meaningful functional abilities, including communication, ambulation and self-feeding

The latest data from the pivotal Transpher A and long-term follow-up studies will be presented at WORLDSymposium™ 2025

NOVATO, Calif., Feb. 05, 2025 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced new data demonstrating treatment with UX111 (ABO-102) AAV gene therapy led to a statistically significant improvement in the Bayley-III[i] raw scores for the subdomains of cognition, receptive communication and expressive communication in patients with Sanfilippo syndrome type A (MPS IIIA) compared to natural history data from untreated patients. These clinical endpoints were correlated with substantial and sustained reduction in levels of heparan sulfate (HS) in cerebrospinal fluid (CSF). These data will be presented at the WORLDSymposium™ 2025 21st Annual Research Meeting, taking place February 3-7 in San Diego.

“These very promising results are particularly gratifying to me as an investigator because this program began at Nationwide Children’s Hospital in the lab of our former center faculty members, Doug McCarty and Haiyan Fu, more than a decade ago. This is a devastating disorder, and it is quite meaningful to see not only this vector’s impact on biologic markers of the disease but also to see its clinical impact on both younger and older treated patients,” said Kevin Flanigan, M.D., director of the Jerry R. Mendell, M.D. Center for Gene Therapy at Nationwide Children’s.

Following treatment with UX111 ($3x10^{13}$ vg/kg), levels of CSF-HS decreased within the first month post-treatment in all patients (N=27) irrespective of age or stage of disease progression at the time of treatment. As of the August 2024 cutoff date, the median reduction in CSF-HS exposure was 65% (p<0.0001) in all patients treated with the $3x10^{13}$ vg/kg dose and 66% (p<0.0001) in the modified intention to treat (mITT) group (N=17). The mean duration of follow-up post-treatment was 34 months for all patients and 36 months for the mITT group with the longest follow-up being 77 months.

Function improved in mITT group compared to natural history

Cognitive function, expressive and receptive communication and fine and gross motor skills were measured using Bayley-III and compared to natural history data from untreated patients with reported rapid progressor phenotypes.[ii] Mean observed raw scores on the Bayley-III domains improved compared to natural history. The model-based mean Bayley-III cognitive raw score from ages 24 to 60 months in the mITT group improved by +16 points compared to natural history patients who declined by -6.8 points, demonstrating a +22.7 point (p<0.0001) treatment effect.

The raw scores were also significantly improved for model-based mean receptive and expressive communication (p<0.05) and fine motor function (p=0.05), while gross motor scores achieved numerical improvements. Gross motor function is generally lost later in the disease progression, and longer-term follow-up is needed to establish significant separation from the natural history data in untreated patients.

Furthermore, there was a statistically significant correlation between CSF-HS exposure and estimated yearly rate of change (EYC) for all five Bayley-III subdomains.

“When we compare the impact of UX111 to natural history in children 2 to 5 years of age, we see that as you correct the underlying enzymatic deficiency at a molecular level, you provide the ability to preserve neurons and for these children to gain new developmental skills,” said Eric Crombez, M.D., chief medical officer at Ultragenyx. “For older patients with severe disease, we know from caregivers and clinicians that stabilizing the disease, so that a child can retain or even slow down the loss of key skills like walking independently, communicating and self-feeding, would have a profound impact on their quality of life.”

Children who are older or with more advanced disease at the time of treatment retained functional abilities

In a pre-specified analysis, all 10 patients that were outside of the mITT group due to older age or having more advanced disease at the time of treatment showed retention of meaningful functional abilities at the time of last assessment. All 10 children, who were between the ages of 5.6 and 14.8 years old at the time of last assessment, retained communication skills (3 verbal and 7 non-verbal), 9 retained ambulation (8 independent and 1 supported) and 9 retained the ability to eat and/or self-feed. These findings are clinically significant as these functions significantly worsen and are eventually lost in late childhood and early adolescence.[iii]

Safety profile remains favorable

UX111 was generally well tolerated across all doses (N=33), including the highest dose of $3x10^{13}$ vg/kg. The most frequently reported treatment-emergent adverse events (TEAEs) to date were elevations in liver enzymes and the majority of these events were mild (Grade 1) or moderate (Grade 2) in severity and all resolved.

These data were included in the Biologics License Application (BLA) submission to the U.S. Food and Drug Administration (FDA) seeking accelerated approval for UX111 that was filed by the company in December 2024. A Prescription Drug User Fee Act (PDUFA) decision on the application and potential U.S. launch are expected in the second half of 2025.

About the UX111 Clinical Program

The *Transpher A* study (NCT02716246) 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 up to age 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.

A separate study (NCT04088734) enrolled five patients. All participants received the highest dose of $3x10^{13}$ vg/kg.

Subjects who participated in either clinical study were invited to enroll into a long-term follow-up study (NCT04360265). The *Transpher A* and long-term follow-up studies 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 in vivo gene therapy in Phase 1/2/3 development for Sanfilippo syndrome type A (MPS IIIA), a rare fatal lysosomal storage disease with no approved treatment that primarily affects the brain. UX111 is designed to be dosed in a one-time intravenous infusion using a self-complementary AAV9 vector to deliver a functional copy of the *SGSH* gene to cells. The therapy is designed to address the underlying *SGSH* enzyme deficiency responsible for abnormal accumulation of heparan sulfate, a glycosaminoglycan, in the brain that results in progressive cell damage and neurodegeneration. 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 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 brain and is characterized by rapid neurodegeneration, with onset in early childhood. Children with MPS IIIA present with global developmental delay which eventually leads to progressive cognitive, language and motor decline, behavioral abnormalities and early death. MPS IIIA is estimated to affect approximately 3,000 to 5,000 patients in commercially accessible geographies with a median life expectancy of 15 years. 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 the observed rapid neurodegeneration that is associated with the disorder.

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 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 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-/mycompany/).

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[i] Bayley-III is the Bayley Scales of Infant and Toddler Development 3rd edition (BSITD III)
[ii] Shapiro et al., 2016; Wijburg et al., 2022
[iii] Delgaldillo et al., 2013