Ultragenyx Announces Positive Interim Phase 1/2 Data in Patients with Angelman Syndrome After Treatment with GTX-102

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Expansion Cohorts showed rapid, clinically meaningful improvement across multiple domains; improvements consistent or exceeding Dose-escalation Cohorts data at Day 170

Additional long-term data in Dose-escalation Cohorts showed increasing and sustained clinical benefit through Day 758

Company will host investor call at 8:00 a.m. ET

NOVATO, Calif., April 15, 2024 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) today announced new data from the Phase 1/2 study of GTX-102 for the treatment of Angelman syndrome. Patients in Expansion Cohorts A & B treated with a set dose and regimen of GTX-102 showed rapid and clinically meaningful improvement across multiple domains consistent with or exceeding Dose-escalation Cohorts 4-7 data at Day 170. Treatment of the Dose-escalation Cohorts 4-7 showed long-term increasing and sustained clinical benefit far exceeding Natural History data at Day 758. These data will be discussed in more detail in a corporate presentation being hosted by the company today at 8:00 a.m. ET and will also be presented by Kemi Olugemo, M.D., FAAN at the 76th Annual American Academy of Neurology Meeting (AAN) in Denver on Tuesday, April 16.

“There is currently no approved disease modifying treatment for Angelman syndrome, which results in profound impairment in individuals living with this disease,” said Erick Sell, M.D., director of the Angelman clinic at the Children’s Hospital of Eastern Ontario, and a principal investigator on the Phase 1/2 study. “The multidomain improvement in the Bayley-4 and ASA measures are significant and in line with the clinically meaningful change observed by patient families. These kids have continued to make functional gains over time, which may ultimately lead to more independence.”

New Expansion Cohorts A & B data include Day 170 results on 24 patients, and long-term Dose-escalation Cohorts 4–7 data include up to Day 758 results on 15 patients.

Expansion Cohorts at Day 170:

- Cognition assessed by Bayley-4 showed rapid and clinically significant improvement compared with Natural History data. Day 170 data were consistent with the treatment benefit observed in the Dose-escalation Cohorts at a similar timepoint.
- Behavior assessed by the Angelman Severity Assessment (ASA) showed rapid improvement exceeding the treatment benefit observed in the Dose-escalation Cohorts at Day 170.
- Hyperactivity and noncompliance assessed by the Aberrant Behavior Checklist-Community (ABC-C) showed rapid and clinically significant improvement at Day 170 compared with Natural History data, providing further insight into one of the most commonly reported behavioral issues.
- Sleep assessed by ASA showed rapid and clinically meaningful improvement exceeding treatment benefit observed in the Dose-escalation Cohorts at Day 170.
- Receptive communication assessed by Bayley-4 showed rapid improvement compared with Natural History data. Day 170 data were consistent with the treatment benefit observed in the Dose-escalation Cohorts at a similar timepoint.
- Gross Motor function assessed by ASA showed rapid improvement exceeding the treatment benefit observed in the Dose-escalation Cohorts at Day 170. Gross motor assessments as measured by Bayley-4 were not performed at Day 170 in the Expansion Cohorts to reduce patient testing burden and are not included in this analysis at this timepoint.
- Multi-domain Responder Index (MDRI) analysis across the four domains of Cognition, Receptive Communication, Behavior and Sleep resulted in a total net response of +2.0 (p-value <0.0001). The majority of patients had already achieved a total net response of +2 to +4 domains, demonstrating improvement exceeding the minimally important difference (MID) threshold in several domains even at this early Day 170 timepoint.

Dose-escalation Cohorts up to Day 758:

- Cognition assessed by Bayley-4 showed continuing long-term improvement compared with Natural History data and exceeded the threshold of clinical significance by many-fold in many patients.
- Behavior assessed by ASA showed continuing clinically meaningful improvement.
- Sleep assessed by ASA showed sustained clinically meaningful improvement.
- Receptive communication measured by Bayley-4 showed sustained and clinically significant improvement compared with Natural History data.
- Gross motor function assessed by Bayley-4 showed continued and clinically significant improvement compared with previously reported Natural History data.
- MDRI analysis across the four domains of Cognition, Receptive Communication, Behavior and Sleep resulted in a total net response of +2.0 (p-value = 0.0007) at Day 338. The majority of patients had a total net response of +2 to +4, as well as a 2- to 5-fold improvement over the MID threshold in several domains.

“The totality of these interim data demonstrates that treatment with GTX-102 resulted in rapid, multi-domain improvements that continued during maintenance dosing. These broad developmental gains are having a meaningful impact on patients and their families. For example, we’re hearing about children who are now able to routinely communicate their needs to family members, which greatly improves their ability to interact with their caregivers. We have also heard from families about their children who are accumulating additional developmental gains such as running, swimming and independent eating,” said Eric Crombez, M.D., chief medical officer at Ultragenyx. “Our next step is an end of Phase 2 meeting with the FDA and interactions with other health authorities to enable timely initiation of a Phase 3 pivotal study.”

There were no unexpected serious adverse events. Three patients had serious adverse events (mild to moderate) of lower extremity weakness assessed as related to study treatment; one in Cohort 7, two in Cohorts A & B; none reported in Cohorts C–E to date. All resolved rapidly without sequelae and remain in the study without ongoing safety concerns. The five original patients affected by lower extremity weakness from Cohorts 1–3 have been re-dosed safely multiple times and are receiving maintenance treatment without recurrence. The Cohort 7 patient has also been re-dosed safely multiple times and is receiving maintenance treatment without recurrence. The two patients in Cohorts A & B remain in study and are expected to continue dosing. The FDA and other regulatory agencies were notified of all safety events and raised no issues nor required additional actions. The foregoing safety information is current as of April 5, 2024.

Conference Call and Webcast Information

Ultragenyx will host a conference call at 8:00 a.m. ET today to discuss the new efficacy and safety data from the GTX-102 Phase 1/2 clinical study. The live and replayed webcast of the call will be available through the company's website at https://ir.ultragenyx.com/events-presentations.

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 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 Cohorts 4-7 (dose-escalation) 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 the Angelman Syndrome Natural History Study

The Angelman Syndrome Natural History Study (NCT00296764) is a multisite, prospective, observational study. The study data are combined with clinic and registry data and stored in the Linking Angelman and Dup15q Data for Expanded Research (LADDER) database platform, which is managed by Boston Children's Hospital and spans different Angelman syndrome cohorts. The Natural History study populations analyzed for comparative purposes to GTX-102 are a subset of the larger populations, and only include 4- to 17-year-old gene deletion patients. These data are illustrative only; differences exist between study designs, subject characteristics and geographical regions and caution should be exercised when comparing data across studies. Natural history data are not available for the ASA assessments.

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 Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 21, 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