Ultragenyx and GeneTx Provide Program Update on GTX-102 for Angelman Syndrome Including Promising Interim Data from Phase 1/2 Study

July 18, 2022

Doses up to 10 mg show good tolerability and meaningful clinical activity in multiple domains

U.K. and Canadian health authorities approved escalation to higher doses

Ultragenyx exercises option to acquire GeneTx for $75 million upfront payment

Conference call to discuss update planned for 5 p.m. Eastern Time

NOVATO, Calif., July 18, 2022 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE) and GeneTx Biotherapeutics LLC today provided a program update on GTX-102 for the treatment of Angelman syndrome (AS), including encouraging interim data from the open-label, dose-escalating Phase 1/2 study in pediatric patients who have a genetically confirmed diagnosis of full maternal UBE3A gene deletion. Interim results on 9 patients from the U.K./Canada arm and 2 patients from the U.S. arm of the Phase 1/2 study demonstrate a meaningful improvement in clinical disease and an acceptable safety profile. These interim data supported a protocol amendment to the Phase 1/2 study that was approved by the U.K. and Canadian health authorities in May 2022 to initiate additional, new cohorts of patients at higher monthly loading doses. The study has begun to enroll under the amended protocol and has dosed the first patient in these new cohorts.

Ultragenyx also announced it has exercised its option to acquire GeneTx and has closed on the acquisition for an upfront payment of $75.0 million plus future milestone and royalty payments.

“We are seeing encouraging early clinical activity across multiple domains and multiple measurements without any evidence of drug-related safety issues. The therapeutic effect should be further enhanced by starting at higher monthly loading doses that have already been shown to be tolerated,” stated Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. “These data combined with the excellent science of Dr. Scott Dindot, the inventor of GTX-102, have given us the confidence to exercise our option to acquire GeneTx at an earlier timepoint so that we can take the lead on advancing GTX-102 into late-stage development for Angelman syndrome.”

"I am convinced we are seeing evidence of a therapeutic effect with GTX-102 though it's still early in the study,” said Erick Sell, M.D., Associate Professor of Neurology and Director of the Angelman clinic at the Children's Hospital of Eastern Ontario, and primary investigator on the study. “I am also encouraged by the improvements in quality of life that most of the families at my center are consistently reporting and believe that this could be a promising treatment for patients with Angelman syndrome."

Study Design and Dosing
The protocol approved in the U.K. and Canada permitted enrollment of up to 12 patients; the companies completed enrollment at 6 patients in the younger Cohort 4 and capped enrollment at 4 patients in the older Cohort 5 based on early encouraging safety and efficacy data in order to amend the protocol and begin dosing newly enrolled patients at higher levels. As of the data cut off, 9 of these 10 patients dosed had reached study Day 128 or further.

Six patients in younger Cohort 4 initiated dosing at 3.3 mg and 4 patients in older Cohort 5 initiated dosing at 5 mg. Patients were titrated on an individual basis. Four patients of the younger Cohort 4 reached the first pre-maintenance dose (PMD) visit at Day 170 and received 7.5 mg doses, and one of these patients reached the second PMD dose at 10 mg. Data were available on 3 patients through the first PMD visit by the data cutoff. Three of the older Cohort 5 patients reached the first PMD dose and received 10 mg doses, and one of these patients had data available by the data cutoff.

The protocol approved in the U.S. permitted enrollment of up to 8 patients enrolled into two groups, an active and an age-matched comparator group. Four patients ages 4 to ≤8 years old have received 4 monthly 2 mg doses of GTX-102 and 2 patients had Day 128 data available at the time of analysis.

Interim Safety Results
There have been 14 patients to receive treatment thus far, 10 under the U.K. and Canada protocol, and 4 under the U.S. protocol. Of these, 7 patients have received cumulative doses over 20 mg, and 13 patients have over 147 days of exposure to treatment. There have been no treatment-related serious adverse events of any type nor adverse events related to lower extremity weakness observed in these patients. The most common adverse events in the U.K./Canada Cohorts (Cohorts 4 and 5) were vomiting (5/10), COVID (4/10), upper respiratory infection (3/10) and transient back pain (2/10). In the U.S. Cohort, 2 of 4 patients had no adverse events, a third had transient difficulty in sleeping and the fourth patient had emesis, upper respiratory infection, and asymptomatic EBV hepatitis that resolved and the patient resumed dosing.

Cerebrospinal fluid (CSF) protein levels have remained stable throughout the course of the study consistent with absence of inflammation. There was one case of CSF protein elevation in the U.K./Canada protocol that was due to an asymptomatic reactivation of Varicella Zoster Virus. The protein normalized and the patient resumed dosing without any issues. One subject in the U.S. protocol had a single modestly elevated CSF protein that resolved on the subsequent assessment.

Interim Efficacy in Cohorts 4 & 5 (9 of 10 patients evaluable)
The “AS Change Scale” (Clinical Global Impression of Change, or CGI-C-AS) and the “AS Severity Scale” (Clinical Global Impression of Severity, or CGI-S-AS) are clinician assessments used to assess patients across five domains (sleep, behavior, communication, gross motor, and fine motor skills) and overall change. The AS Change Scale is a relative scale of improvement, and the AS Severity Scale is an objective scale with criteria for each change in domain severity.

AS Change Scale evaluations at Day 128 show 7 out of 9 patients improved from Baseline in at least 3 of 5 domains and in the overall score. These data are supported by the AS Severity Scale evaluations taken at Baseline and Day 128 where 6 patients exhibited a decrease in severity in at least 2 of 5 domains and in the overall score.

Furthermore, one patient from Cohort 4 showed a 2 or 3-point improvement in the AS Severity Scale across all 5 domains at the PMD assessment at Day 170. This suggests continued improvement from Day 128 prior to receiving the fifth dose.

These promising improvements in the AS Change and Severity Scale scores were also supported by the other clinical measurements including the Bayley Scales of Infant and Toddler Development (Bayley-4), which is administered by a trained psychologist; the Vineland-3 adaptive behavior scale, which is administered by a clinician; and the Observed Reported Communication Ability (ORCA), a caregiver-reported questionnaire.

Interim efficacy in U.S. patients (2 of 4 patients evaluable)
AS Change Scale evaluations taken at Baseline and Day 128 in 2 patients show both had relative improvement from baseline in at least 3 of 5 domains and overall. These data were supported by AS Severity Scale evaluations taken at Baseline and Day 128 where both patients exhibited a decrease in severity in at least 2 of 5 domains and overall.

"We are treating severely developmentally impaired individuals who are non-verbal and normally have a very slow rate of learning, making only minimal progress over years based on clinical observations and natural history studies," stated Elizabeth Berry-Kravis, M.D., Ph.D., Professor, Pediatrics at Rush University Medical Center and primary investigator on the study. "The changes that we have seen clinically in less than a year in both the original five patients and the current patients, which are also captured by the AS Change and Severity Scales, may seem small but are truly important improvements, given the rate of developmental progress in Angelman syndrome."

Domain-specific assessments
Multiple domain specific assessments and caregiver interviews supported AS Change (CGI-C-AS) and Severity (CGI-S-AS) Scale results. Changes in the functional domains of Sleep, Behavior, Communication, Gross Motor and Fine Motor skills across the patients demonstrated positive clinical activity of GTX-102.

Management will be joined by investigators Dr. Sell and Dr. Berry-Kravis to provide a detailed summary of the data across these domains on today's investor conference call.

Study Amendment and Dose Escalation
Under the new study amendment approved in the U.K. and Canada, additional dose-selection cohorts will sequentially enroll new patients at incrementally higher starting doses ranging from 7.5 to 14 mg based on age. A younger Cohort 6 will begin dosing at 7.5 mg and an older Cohort 7 at 10 mg. Once clinically sufficient efficacy is observed, two expanded cohorts will enroll 20 patients in each age range using the optimal dosing algorithm determined from the dose-selection cohorts. These patients would provide the longer-term efficacy and safety information for the program. Ultragenyx will seek to initiate the amended protocol in the U.S. pending discussions with the FDA.

In the Maintenance phase, patients from all cohorts will receive treatment with GTX-102 once every 3 months after the patient's last monthly dose of GTX-102, with incremental dose escalations possible to a maximum dose of 14 mg based on achieving an adequate clinical response.

Investor Conference Call and Webcast Information
Ultragenyx will host an investor conference call today, Monday, July 18, 2022, at 2 p.m. PT / 5 p.m. ET to discuss the results. The live and replayed webcast of the call will be available through the company's website at https://ir.ultragenyx.com/events-presentations. To participate in the live call, please register by clicking on the following link (registration link), and you will be provided with dial in details. The replay of the call will be available for one year.

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, 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 typically not inherited but instead occurs spontaneously. It is estimated to affect 1 in 12,000 to 1 in 20,000 people globally.

Individuals with Angelman syndrome have developmental delay, communications issues, balance issues, motor impairment 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. While 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 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 show that GTX-102 reduces the 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 U.S. Food and Drug Administration (FDA). In August 2019, GeneTx and Ultragenyx announced a partnership to develop GTX-102, with Ultragenyx receiving an exclusive option to acquire GeneTx.

About Ultragenyx Pharmaceutical Inc.
Ultragenyx is a biopharmaceutical company committed to bringing novel products to patients for the treatment of serious rare and ultra-rare 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.

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 business plans and objectives for GTX-102, the therapeutic potential and clinical benefits of GTX-102, expectations regarding the safety and tolerability of GTX-102, and future clinical 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, 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 ability of the company to successfully develop GTX-102, the effects of the COVID-19 pandemic on the company's clinical activities, business and operating results, , uncertainty and potential delays related to clinical drug development, the risk that clinical outcomes demonstrated in interim data from our clinical trials may materially change or increased incidents of adverse events as patient enrollment continues and/or more patient data becomes available, the company's ability to achieve its projected development goals in its expected timeframes, risks and uncertainties related to the regulatory approval process, smaller than anticipated market opportunities for the company's products and product candidates, manufacturing risks, competition from other therapies or products, our ability to integrate acquired products or businesses, 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 on May 6, 2022, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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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