GeneTx and Ultragenyx Announce Positive Interim Phase 1/2 Data on Investigational GTX-102 Demonstrating Improvement in Patients with Angelman Syndrome

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Efficacy in multiple functional measures observed in all five patients treated

Highest doses associated with a significant but reversible safety issue

Study amendment planned to focus on lower end of dose range

Conference call to discuss results planned for 5pm Eastern Time

SARASOTA, Fla. and NOVATO, Calif., Oct. 26, 2020 (GLOBE NEWSWIRE) -- GeneTx Biotherapeutics LLC and Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), companies partnered in the development of intrathecally administered GTX-102, an investigational treatment for Angelman syndrome, today announced positive interim data from the Phase 1/2 study of GTX-102. Preliminary results from the first five patients treated indicate substantial improvements in all patients in at least two disease domains including communication, behavior, sleep, gross motor function, and fine motor function as measured by the Clinical Global Impression of Improvement Scale for Angelman Syndrome (CGI-I-AS) at day 128. At the highest doses, all five patients experienced a serious adverse event (SAE) of lower extremity weakness believed to be related to local inflammation due to GTX-102. Following these events, the companies paused enrollment and dosing. These SAEs were assessed as mild or moderate in severity and have generally improved over a period of a few weeks while disease domain improvements have been sustained for three months. The study protocol will be amended to reduce the dose-level range and modify the administration process, which is expected to reduce further drug-related SAEs.

“The work that the GeneTx team and Dr. Scott Dindot and his lab have conducted over these last years provided the opportunity to impact Angelman syndrome in a fundamental manner with a potent antisense oligonucleotide,” noted Emil D. Kakkis, M.D., Ph.D., CEO and President of Ultragenyx. “These initial GTX-102 findings raise the possibility of improving some of the significant symptoms of Angelman syndrome.”

“The *UBE3A* antisense transcript targeted by GTX-102 is a viable target for treatment,” stated Scott Stromatt, M.D., Chief Medical Officer of GeneTx. “The results observed to date are encouraging and we look forward to resuming dosing at lower doses to help avoid side effects.”

“So far we are seeing rapid improvements in multiple areas, including some kids doing things they’ve never done before, and I don’t believe this rate of progress in development skills has been seen before in Angelman syndrome,” commented Elizabeth M. Berry-Kravis, M.D., Ph.D., Professor of Pediatrics, Neurological Sciences and Biochemistry, Rush University Medical Center, and investigator in the GTX-102 clinical study. “It is especially amazing that families are asking me repeatedly when they can start treatment again despite the side effects that their child experienced. That speaks to the value of what they were seeing in their child.”

Interim Efficacy Results

The study design includes five dosing cohorts in which patients were to receive four monthly doses of GTX-102 on an intra-patient dose escalation scheme. Five patients between the ages of 5 and 15 with deletions in the maternal *UBE3A* gene region were enrolled in the first three cohorts and are included in the interim data analysis.

Initial indications of benefit have been observed in all five treated patients across the key domains of communication, fine and gross motor skills, behavior, and sleep as measured by the CGI-I-AS. In some patients these initial indications of clinical improvement were observed by the investigator early in the study at the two lowest dose levels and began within weeks of the first dose.

At day 128, all patients had a meaningful improvement in their individual global CGI-I-AS score, which evaluated overall improvement across five domains specific to the symptoms of Angelman syndrome. All five patients were assessed as ‘much improved’ or ‘very much improved’ on the 7-point global scale of -3 to +3 with a mean change of +2.4. All patients had at least two symptom domains that were assessed as ‘very much improved’ or ‘much improved’ and at least three domains that were

‘minimally improved’ or better (Score of 3, 2, or 1).

Patient-by-patient CGI-I-AS results by domain and overall are as follows:

Patient	Overall Global Rating	Sleep	Behavior	Communication	Gross Motor	Fine Motor
001	+2 Much Improved	0	+1	+2	+2	0
002	+3 Very Much Improved	0	+1	+3	-2*	+3
003	+2 Much Improved	+2	+2	+1	-1*	0
004	+2 Much Improved	0	+3	+2	-1*	+2
005	+3 Very Much Improved	+3	+1	+3	+2	+2

**Patients 002, 003, and 004 had gross motor impairment at time of assessment due to the ongoing SAE*

Note: CGI-I-AS scale ratings: +3: very much improved, +2: much improved, +1: minimally improved, 0: no change, -1: minimally worse, -2: much worse, -3: very much worse.

Data as of day 128, except day 86 for patient 005.

Supporting the CGI-I-AS improvements were changes in other domain-specific measurable endpoints. All patients experienced numerical increases in the sub-scale growth scores of expressive and/or receptive communication of the Bayley Scales of Infant and Toddler Development (Bayley-4) domains, and three patients showed improvements in the Observed Reported Communication Ability (ORCA) measure of expressive, receptive, and pragmatic communication.

The interim analysis did not include data from other exploratory outcome measures such as seizure frequency, sleep diaries, EEG patterns, UBE3A protein levels in the CSF, ambulation by wearable device, and adaptive behaviors.

Caregiver reports, via functional domain questionnaire, of improvement in the patients also support the changes seen in CGI-I-AS and the other endpoints. Notable caregiver-reported changes include:

- Acquisition of spoken words, signs and gestures, and augmentative and alternative communication abilities; two previously nonverbal patients began using words, one reaching nine words
- Ability to respond to their name, follow commands, and focus on tasks
- Acquisition of independent capabilities, such as self-feeding with a fork
- Increased abilities in physical activities, such as patients swimming on own and catching/throwing a ball
- Dramatically improved sleep
- Decreased maladaptive behaviors
- Increased social engagement
- Improved gait and posture

Interim Safety Results

Significant but reversible lower extremity weakness has been observed as a grade 1 or 2 SAE in four patients after administration of the highest dose, which was approximately 10 times higher than the initial low dose of cohort 1, and in one patient after administration of a single dose at the second highest dose level assessed, which was approximately 6 times higher than the initial low dose of cohort 1. The SAE was not observed after the two lower starting doses in the first four patients.

The onset began between approximately one to four weeks after the last dose. In two patients the lower extremity weakness progressed to an inability to walk or bear weight. No patients experienced upper extremity weakness. The companies paused all dosing beginning at the time of the first SAE, and patients were treated with intravenous immunoglobulin (IVIg) and

corticosteroids. The most severe aspects of the neurologic findings steadily and substantially resolved within a few weeks of the dosing pause and implementation of treatment. The adverse event has completely resolved in four patients (occurring between 19 and 70 days from onset), while the findings in the one remaining patient substantially improved by three to four weeks and is now almost fully resolved.

The lower extremity weakness was associated with an elevation of cerebrospinal fluid (CSF) protein, which has been reported in studies of other intrathecally administered antisense oligonucleotides. Magnetic resonance imaging (MRI) shows findings consistent with local inflammation in the meninges and nerve roots in the region of intrathecal administration in the lower back (lumbosacral region) at the higher doses of GTX-102. The lower extremity SAE was not observed at lower doses and the delayed events of lower extremity weakness were not observed in preclinical GLP toxicity studies at similar and higher doses.

There have been no other SAEs reported to date with GTX-102. Other adverse events have included transient ataxia, headache, and fatigue. The acute, transient ataxia was reported in all five patients, occurred two to six hours after the intrathecal injection, lasted for 24 to 72 hours, and was dose dependent. No patients have withdrawn from the study.

Study Next Steps

The companies paused dosing and enrollment in the study after first observing the lower extremity SAE to evaluate the event, assess efficacy, and monitor recovery. After review of all findings and nonclinical evaluations, the study protocol will be amended to try to reduce exposure to GTX-102 at the point of local contact during intrathecal administration. The dose will be lowered to the observed safe range at which clinical improvement was first observed and a slower titration regimen will be implemented that is dependent on individual patient response and age. The administration method will be modified to help reduce local drug contact time. The companies will obtain agreement on these modifications with the U.S. Food and Drug Administration (FDA) prior to resuming enrollment and dosing. Further detail from the first five patients will be presented at the Foundation for Angelman Syndrome Therapeutics (FAST) Global Summit in December 2020. Additional safety and efficacy data from the study are expected in 2021.

Investor Conference Call and Webcast Information

Ultragenyx will host an investor conference call today, Monday, October 26, 2020, 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.cfm. To participate on the live call by phone, dial (855) 797-6910 (USA) or (262) 912-6260 (international) and enter the passcode 5684773. 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, 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 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 GeneTx Biotherapeutics

GeneTx Biotherapeutics LLC is a startup biotechnology company singularly focused on developing and commercializing a safe and effective antisense therapeutic for the treatment of Angelman syndrome. GeneTx was launched by FAST, a patient advocacy organization and the largest non-governmental funder of Angelman syndrome research. GeneTx licensed the rights to antisense technology intellectual property from the Texas A&M University System in December 2017.

About Ultragenyx

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

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, 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 Company's ability to successfully develop GTX-102 at lower doses, including the resolution of adverse events that were seen at higher doses, whether lower doses of GTX-102 are sufficiently effective to support the continued development of the program, the effects from the COVID-19 pandemic on the company's commercialization activities, business and operating results, smaller than anticipated market opportunities for the company's products and product candidates, manufacturing risks, competition from other therapies or products, uncertainties related to insurance coverage and reimbursement status of the company's newly approved products, the company's evolving integrated commercial organization, 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 July 30, 2020, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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