



GeneTx and Ultragenyx Announce Presentation of Phase 1/2 Data on Investigational GTX-102 in Patients with Angelman Syndrome

December 5, 2020

Results presented at Foundation for Angelman Syndrome Therapeutics (FAST) Global Summit

Additional data, including EEG findings, support prior initial indications of activity and there were no new adverse events

SARASOTA, Fla. and NOVATO, Calif., Dec. 05, 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 the presentation of data from the Phase 1/2 study of GTX-102 at the Foundation for Angelman Syndrome Therapeutics (FAST) Global Summit. Details regarding the scientific basis for GTX-102 targeting in Angelman syndrome were presented along with additional supportive clinical data on EEG and other endpoints, along with further description of the safety events. Additional nonclinical study data were included showing substantial silencing activity at low repeat doses along with chronic nonclinical safety data at higher doses compared to dosing in the human study. Presentations were made by Scott Stromatt, M.D., Chief Medical Officer of GeneTx and Elizabeth M. Berry-Kravis, M.D., Ph.D. Professor of Pediatrics, Neurological Sciences and Biochemistry at Rush University on Friday December 4th, and by Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx, on Saturday, December 5th.

"I am excited by the preliminary findings presented at the FAST scientific symposium. A tremendous amount of work was put into understanding the *UBE3A-AS* transcript and developing GTX-102, so it is great to see how those efforts have translated into initial indications of effect in the clinical study in patients with Angelman syndrome," said Scott V. Dindot, Ph.D., Associate Professor, Texas A&M University, and Executive Director, Molecular Genetics at Ultragenyx. "I am grateful to be a part of this endeavor, and I look forward to seeing what the future holds for the Angelman syndrome community."

"GTX-102 demonstrates a paternal *UBE3A* gene targeting strategy can result in substantial clinical activity and in a more rapid time frame than we expected," stated Dr. Scott Stromatt. "We better understand the serious adverse events reported with GTX-102 at higher doses and we see a way forward to redose patients and to enroll new patients into the clinical trial. We are working with FDA to reach agreement on a modified trial design."

Study Design and Dosing

Five patients in three dose cohorts were enrolled who all had deletions in the *UBE3A* locus as the cause of Angelman syndrome and were treated with a monthly intrathecal dose of GTX-102 that increased for each of the first four doses provided to each patient. Two patients in cohort 1 received a monthly ascending dose sequence of 3.3 mg, 10 mg, 20 mg, and 36 mg, with the first patient receiving one additional fifth dose in an extension amendment at the 36 mg level. Two patients in cohort 2 received three sequential monthly doses of 10 mg, 20 mg, and 36 mg. One patient in cohort 3 received a single dose of 20 mg. Further dosing was stopped once the first serious adverse event occurred, as previously described.

Pharmacokinetic results indicate that plasma levels of GTX-102 were dose proportional. GTX-102 was not detectable in the blood or cerebrospinal fluid (CSF) in samples taken one month after the last dose and prior to subsequent monthly doses, indicating that the drug did not accumulate in the blood or CSF.

Interim Efficacy Results

Previously disclosed improvements in the Clinical Global Impression of Improvement Scale for Angelman Syndrome (CGI-I-AS) were presented along with detailed individual results for both global scores and individual domains. The mean change was +2.4 in the CGI-I-AS global score and all patients had at least 3 domains of improvement and 2 domains of much improved or very much improved at this interim assessment.

Communication

Communication was one of the most impaired functions in these five patients based on baseline scores and is the most important disease domain for families according to a recently published disease concept model¹. Detailed scores from the communication domain of the CGI-I-AS showed much improved or very much improved scores in four of five subjects along with supportive

detailed data from other scores. In the Bayley Scales of Infant and Toddler Development (Bayley-4), multiple patients improved on receptive or expressive communication sub-scales. In the Observed Reported Communication Ability (ORCA) measure of expressive, receptive, and pragmatic communication, three patients, ages 5, 10, and 15, demonstrated clinically relevant increases at day 128 and two patients did not have notable changes.

EEG and Seizures

At baseline, all patients had stable seizure control per protocol requirements and did not have reports of seizures as adverse events during the study. Blinded independent central electroencephalogram (EEG) readings were conducted at baseline and day 128 (day 86 for patient 5) for four of five treated patients to assess delta waves and epileptiform discharges among other findings common in Angelman syndrome. Qualitative readings of the EEGs indicate decreases in the prevalence of notched delta waves in three of the four evaluated patients with patient 1 showing minimal change or a slight increase. Decreases in the prevalence of epileptiform discharges were also observed in three of the four evaluated patients with patient 5 showing minimal change or a slight increase. Quantitative analysis of the EEGs completed to date in the first two patients showed decreases in relative delta power (2-4 Hz) in both evaluated patients after beginning GTX-102. These are preliminary findings and, due to normal variability in EEG tracings, the assessments will be repeated after longer-term treatment with GTX-102.

Gross Motor and Fine Motor

Preliminary readings from the ActiMyo device that measures hourly distance walked, stride length, and stride speed, support the utility of this functional measure. One patient, who initially had a decrease in distance walked due to the lower extremity weakness SAE, later was able to exhibit a meaningful increase from baseline as the SAE resolved. Other improvements in fine motor function previously disclosed were presented.

Length of Effect

The clinical changes observed appear to last at least 3 to 5 months from the last dose. To date, most of the subjects have retained many caregiver-reported clinical changes observed but some patients are observed to be experiencing some loss of effect. The long period of observed clinical response post-dose would support use of a maintenance dosing regimen of every 3 months, if an appropriate and safe dosing regimen is identified.

Additional Interim Safety Results

As previously reported, all patients had a grade 1 or 2 serious adverse event (SAE) of lower extremity weakness associated with local inflammation in the region of intrathecal administration in the lower back at the higher doses of GTX-102. The SAE has fully resolved in all five patients.

The SAE occurred between 6 and 30 days after the last infusion of 36 mg in four patients and 20 mg in one patient. In patient 1, the SAE was not observed until after the second dose at the 36 mg level. Clinical improvements observed in the study have been sustained beyond resolution of the SAE and the negative impact of the SAE on gross motor function in certain patients has recovered with resolution of the SAE.

No new adverse events have been reported since the last update. No patients have withdrawn from the study.

Additional Nonclinical Data

Results from additional non-human primate (NHP) studies were also reported including both single dose and repeat dose studies conducted for as long as six months. Toxicology assessments indicated acute clinical observations including sporadic transient lower limb weakness generally resolving by 24 hours after dosing. There was no observation throughout these studies of delayed-onset weakness similar to the human study SAE, which included single doses as high as 10 mg (equivalent to a dose in humans of approximately 110 mg) or at repeat monthly doses as high as 5 mg (human equivalent of approximately 56 mg per dose). No kidney or platelet toxicities were observed in the NHP studies.

The NHP studies also assessed knockdown of the *UBE3A*-antisense (*UBE3A-AS*) transcript, the RNA that inhibits expression of the paternal *UBE3A* allele in Angelman syndrome. Monthly dosing of GTX-102 showed substantial reduction of the *UBE3A-AS* transcript at monthly doses of 1, 2, and 3 mg. *UBE3A-AS* reduction occurred in multiple brain regions relevant to Angelman syndrome.

Scientific Detail on GTX-102 Targeting

Detail was presented on the GTX-102 target region in the *UBE3A-AS* transcript. Dr. Dindot's work on understanding the molecular genetics of the antisense transcripts allowed the discovery of a more potent place to target an antisense oligonucleotide (ASO) for the knockdown of the repressive antisense RNA transcripts to induce more *UBE3A* expression. The manuscript describing the work performed by Dr. Dindot's laboratory is currently under review.

Update on Clinical Study Next Steps

The companies will propose a plan to the FDA to resume enrollment and dosing in the study which is currently on hold. The proposed plan is to amend the dosing and titration regimen to start at a low dose and titrate individually, based on patient age and response to GTX-102. The maximum dose will be below 20 mg, which is the lowest dose at which the lower extremity weakness SAE was observed. Also, a new administration procedure will be used to minimize duration of exposure at the injection site. The companies aim to resume enrollment as soon as possible following receipt of guidance and approval from the FDA.

1: Willgoss, T. *et al.* Measuring What Matters to Individuals with Angelman Syndrome and Their Families: Development of a Patient-Centered Disease Concept Model. *Child Psychiatry Hum Dev* (2020). <https://doi.org/10.1007/s10578-020-01051-z>

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 October 27, 2020, and its subsequent periodic reports filed with the Securities and Exchange Commission.

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