May 17, 2023

Dear members of Angelman syndrome community,

First and foremost, we hope this update finds you and your families continuing to stay well.

In our effort to keep the community informed on GTX-102, our Angelman syndrome research program, we wanted to share some recent updates.

Today, we announced that the U.S. Food and Drug Administration (FDA) has reviewed and agreed to a change in the protocol, or design, of the Phase 1/2 study of GTX-102 in pediatric patients with Angelman syndrome (AS). This change, or amendment as it's referred to, allows Ultragenyx to use similar dosing ranges for clinical trial participants in the U.S. and outside of the U.S.

With this news, we will be working to open additional trial sites across the U.S. and this process will take several months. We will update clinicaltrials.gov when additional sites are ready to begin enrollment.

We realize that many of you may have questions related to this update, which we hope some of the following information will address.

What is the status of the GTX-102 program?

The GTX-102 program is currently a phase 1/2, open-label, multiple-dose, study to evaluate the safety and tolerability of GTX-102 in pediatric patients with Angelman syndrome. An open-label study means both the physician (Principal Investigator or "PI") and the individual receiving the treatment are aware of the therapy that is being administered. This study also examines additional clinical measures including plasma and cerebrospinal fluid (CSF) concentrations. Patients must be age 4 to 17 years at screening. The study includes a monthly "dosing period", an amount of time for the treatment to reach a certain level in the body, followed by a "maintenance period" to keep that level of therapy at a consistent level.

Have you addressed the safety issue that resulted in changes to the study?

Ultragenyx made a number of changes to the study design to reduce the incidence of leg weakness and inflammation that occurred with high doses of GTX-102 treatment. We have seen a significant reduction in these events with lower doses and other changes to the protocol. The events of leg weakness to date have all been reversible and have not resulted in permanent damage. The potential benefit of receiving GTX-102 remains and Ultragenyx remains committed to rigorous safety monitoring for all children participating in this study.

Where are the clinical sites and when will more open to enroll in the study?

Currently sites are located in U.S., Canada, United Kingdom, and Australia. Additional sites are planned, with each site needing a different amount of time to start up. Each clinical trial site is required to go through its own approval process including ethical review. Some sites might take longer than others, but we are working with sites closely to expedite the process.
Please check https://clinicaltrials.gov/ct2/show/NCT04259281?draw=2 for the latest site list as sites are continually added.

How are interested individuals offered participation in the study?

The Doctor (Principal Investigator or "PI") at each site determines which individuals living with Angelman syndrome are appropriate for participation based on medical history. Please contact trialrecruitment@ultragenyx.com or visit https://clinicaltrials.gov/ct2/show/NCT04259281?draw=2 to locate a site participating in the study once they are active and available to enroll individuals into the study. Each site has an opportunity to enroll participants and will decide how many individuals they can manage at a given time. Ultragenyx does not determine which children are offered participation.

The Ultragenyx AS team would like to express our sincere gratitude to our community partners and the families who have helped us deepen our understanding of Angelman syndrome. We know that time is invaluable in the lives of rare disease patients and families and our goal is to advance research as efficiently and fast as possible while ensuring development of a safe treatment option for AS. As Dr. Emil Kakkis, Ultragenyx's CEO and Founder, expressed at a recent community event, the development of new treatments for rare diseases is hard, and we will all be in this together. Many unforeseen challenges may occur that we must solve to advance research and getting to a safe and effective drug will take time, fortitude, and collaboration with the community.

We understand that you may have additional questions, so please know we'll continue to work with our community partners to make sure we are aware of those questions and try our best to get you the answers that you're looking for over the coming weeks and months. Should you have any specific trial related questions, please reach out to TrialRecruitment@ultragenyx.com. You're also welcome to reach out to PatientAdvocacy@ultragenyx.com with general community related questions.

Sincerely,

The GTX-102 Team