18 August 2022

Update on Rugonersen* (RO7248824) as investigational therapy for Angelman syndrome: Recruitment into the first part of the Phase I TANGELO study has been completed

Dear Angelman Syndrome community,

As part of our ongoing conversation and following your request to receive important and timely updates about Roche/Genentech's Angelman Syndrome (AS) clinical program, today we are pleased to announce that worldwide recruitment has been completed for the first part of the Phase I TANGELO study evaluating **Rugonersen*,** the investigational UBE3A-LNA therapy RO7248824 (RG6091). A total of 50 people living with Angelman syndrome across 4 countries have been recruited and completed dosing in the first part of TANGELO Ph1 study. All the study participants have completed the first part of the TANGELO study, also called Multiple Ascending Dose (MAD), where they received up to 3 doses over a period of 8 weeks. All families were offered to continue into the second part of the TANGELO Ph1 study, also known as Long Term Extension (LTE), which will evaluate different dose levels with long intervals between administrations for a prolonged period of time, currently planned for up to 3 years.

"People living with Angelman syndrome and their families are faced with life changing challenges and uncertainties that are not addressed by current treatments," says Brenda Vincenzi, M.D., Senior Medical Director at Roche. "We are excited that the first part of our Phase 1 clinical trial has completed enrollment and believe it is a critical next step toward the development of a novel therapy that has the potential to transform the treatment landscape for this devastating disease."

This major achievement is a result of the Angelman community's commitment from the beginning of Roche/Genentech's plans to start the development of **Rugonersen** in Angelman syndrome, and we are very grateful to all trial participants, their families, the clinical trial sites and staff, and the broader Angelman community (including patient organizations and academic collaborators) who have supported the design, initiation and recruitment phases of the study.

What happens now that recruitment for the first part of TANGELO is complete? When will results be available?

Whilst recruitment completion of the MAD part of the study is exciting news, the second part of the trial has started. Each trial participant will be offered to continue to undertake tests, medical evaluations, intrathecal injections of the investigational therapy **Rugonersen**, and use several monitoring tools over a 36 month period. Participants' safety and trial experience will be regularly monitored by researchers at trial sites and Roche/Genentech.

Once the second part of the study is completed, researchers will analyze the overall study data, which we expect sometime in 2026. Should the benefit-risk profile of **Rugonersen** appear favorable, data will be submitted to health authorities for consideration for support of further development of the **Rugonersen** clinical program.

If you have any questions about this update, please do not hesitate to contact us.

Sincerely,

Brenda Vincenzi, MD Senior Medical Director PD Neuroscience	Shady Sedhom Global Patient Partnership Director

RG6091 has a new name:* **Rugonersen

Rugonersen is the international non-proprietary name (INN), also known as the generic name, for the investigational molecule most recently known as RG6091.

The INN process is formally run by the World Health Organization and can only be started if an investigational molecule is in the clinical trial testing phase. There are many considerations when applying for an INN, such as using the required word "stem" or name ending that allows healthcare professionals to recognise a similar group of substances (-rsen), sufficient uniqueness from other approved INNs to aid safe prescribing, and if the INN can be utilized and pronounced in multiple languages.

Rugonersen is an investigational medicine not approved for the treatment of Angelman Syndrome by health authorities. If an investigational medicine is ultimately approved by health authorities, a brand name would then be assigned.

Questions and Answers

1. **What is the TANGELO Phase I study?**

   The TANGELO Ph1 study tests an investigational UBE3A-LNA therapy called Rugonersen (**RO7248824**) for AS to evaluate its safety and tolerability, how it is handled by the body, and its effects on core symptoms of AS. We enrolled 50 children between 1 and 12 years old who have a molecular diagnosis of AS, of either a deletion or mutation genotype, in this study.

   The TANGELO Ph1 study is divided into two parts:

   - Multiple Ascending Dose (MAD): Evaluating the safety and tolerability of a different ascending dose levels, starting with very low dose level and
   - Long term extension (LTE): Evaluating different dose levels with long intervals between administrations

   Rugonerse is designed to target the suspected root cause of AS, which is a lack of the UBE3A protein in the brain. All participants are receiving the investigational therapy; no placebo

treatment is administered during the course of this study. We do not know if a child's health will improve by participating in this study, but the information collected from the study may help others with AS in the future.

2. Access to Rugonersen

At this time, Rugonersen is only available through the TANGELO Phase I clinical study. Should results of the study provide a better understanding of the benefits and risks of Rugonersen, we plan to expand research efforts and potentially initiate additional clinical trials.

Our team recognises that the interest in participating in AS clinical research may be greater than the capacity of our development programme, and that not every person nor every capable AS center interested in this clinical study will be able to participate. The TANGELO Ph1 study is the first trial of a broader clinical development programme designed to generate data so that the benefit and risk of Rugonersen can be determined as quickly as possible.

3. Communications about study data

Roche and Genentech are committed to transparent and timely communication, as well as ensuring the integrity of ongoing clinical trial operations and data collection. In line with our Global Policy on Sharing of Clinical Study Information, we will share overall programme updates and relevant data from completed and ongoing clinical studies with the scientific community via appropriate channels (e.g. scientific meetings, peer-reviewed journals, etc.).

Again, we thank the Angelman community for your partnership and continuous support of our research efforts. This is an exciting time for AS research, and we are committed to working together to follow the science and advance the understanding of AS.

4. Can people still join the TANGELO Ph1 study?

Although the recruitment for the first part of TANGELO (the MAD part) has been completed, additional recruitment for the second part of TANGELO (the LTE part) is ongoing for a limited number of new patients.