21 June 2023

Update on Rugonersen (RO7248824), an investigational therapy for Angelman syndrome: Roche initiates search for an external partner to take over the clinical development of rugonersen.

Dear Angelman syndrome community,

Following our commitment to transparently communicate about the Angelman syndrome (AS) clinical programme with rugonersen (RO7248824) and your request to receive timely updates, we would like to share an important update with you. Roche has made the difficult decision not to move forward with a new clinical trial for rugonersen and has initiated the search for an external partner to take over the development of rugonersen.

The primary objective of the ongoing Phase 1 TANGELO study is to evaluate the safety and tolerability of rugonersen. During the interim analysis (looking at the data at a pre-planned point while the study is still ongoing) rugonersen has demonstrated an acceptable safety profile. Although some encouraging effects were observed in the patients' EEG, the observed level of clinical improvements in the TANGELO dosing regimens and as compared to natural history data (the usual course of development of individuals with AS in the absence of treatment) did not meet Roche's internal criteria to move into the next phase of clinical development. Roche is currently looking for external partners to explore the potential of the molecule and who may continue the clinical development of the molecule. It is important to note that this decision was not made because of any safety concerns for rugonersen.

We acknowledge that this decision is unexpected and we want to assure the AS community that Roche is putting all efforts into finding a suitable external partner who can pursue the clinical development of rugonersen. All TANGELO sites were notified of this decision and the principal investigators are in the process of informing all families participating in the TANGELO study. While we cannot speak on behalf of a potential future partner, we are planning to provide rugonersen to the study participants, if they wish, until February 2024.

We would like to acknowledge the tremendous contribution of the families who are participating in TANGELO, as well as the patient advocacy groups, clinical research sites and investigators, and the broader AS community. We remain grateful to all of you for your collaboration and support. We are truly humbled by the incredible resilience of this community.

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

For study participants and their family members, we encourage them to reach out to their study physician for more information and detailed next steps.

Sincerely,

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

Questions and Answers:

1. **Have there been any safety concerns with rugonersen?**

   The decision not to progress rugonersen into the next stage of clinical development is not related to safety reasons.

2. **When are you going to share the exploratory efficacy data from TANGELO?**

   Roche is committed to sharing study results with the scientific and patient community. These will be released in due course via several channels, including manuscripts, and lay patient summaries.

3. **What happens to patients who are currently enrolled in the TANGELO study? Will they continue receiving the investigational therapy, rugonersen?**

   While we cannot speak on behalf of a potential future partner, we are planning to provide rugonersen to the study participants until February 2024.

4. **How will this decision affect the clinical development of Roche's other programs in Angelman and Dup15q Syndrome?**
   Roche has a broad portfolio in neurodevelopmental disorders at different preclinical and clinical stages of development. The decision on rugonersen does not impact the other programmes in our portfolio, including the Ph2 clinical trials with alogabat in Angelman syndrome and basmisanil in Dup15q syndrome.