Rugonersen Community Q&A

Basel, Switzerland, 6 July 2023

Dear Angelman Community,

The Roche team 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.

Roche would like to thank the community for submitting these important questions.

1. We understand that the trial was stopped following an interim analysis of the data. Please comment on what endpoints you assessed, and what you learned from this interim analysis that drove your decision not to move forward with the next study.

    - Roche has taken the decision not to progress rugonersen into the next stage of clinical development.
    - While we cannot speak on behalf of a potential future partner, Roche is planning to continue to provide rugonersen in the ongoing TANGELO study until February 2024.
    - The primary objective of the study was to investigate the safety, tolerability, PK (pharmacokinetics) and PD (pharmacodynamics) of Rugonersen in participants with AS administered via IT (intrathecal) delivery. In TANGELO, rugonersen was safe and adequately tolerated.
    - Beyond safety, tolerability, PK and PD, we have looked into exploratory endpoints, such as the Bayley Scale for Infant Development version 3 (Bayley-3).
    - The observed level of clinical efficacy in TANGELO was insufficient to meet Roche's current internal criteria to move into the next phase of development. However, some elements, including the observed effect on EEG are encouraging, therefore we are currently looking to find a suitable external partner to further explore the potential of the molecule and who may continue its clinical development.

2. Knowing you had a lot of endpoints in this study (e.g. ORCA [Observer Reporter Communication Ability], BSID [Bayley Scale for Infant Development] , VABS [Vineland Adaptive Behaviour Scale] , Sleep Mat, etc) can you explain which were assessed in this interim analysis and which were considered positive and which negative to drive this decision?

- We have looked into exploratory endpoints such as the Bayley-3. Although exploratory, the observed level of clinical efficacy at the doses tested in TANGELO was insufficient to meet Roche's current internal criteria to move into the next phase of development. However, some elements, including the observed effect on EEG are encouraging, therefore we are looking to find a suitable external partner to further explore the potential of the molecule.
- The study had no 'in-study control group' (such as placebo). Therefore, we cannot talk about "positive" or "negative" endpoints. Across various instruments, we observed some improvement that could be explained by treatment effects.

3. Did you do an entrance and exit interview by the caregivers to capture changes that they saw, or did not see, that could have been lost, or not captured, in the endpoints you were using?
    - Particularly with rare diseases, we believe that caregiver involvement is critical at the early stages of drug development and their insights are shaping our work every day.
    - We conducted an entrance interview with the caregiver.
    - Each and every family's caregiver for the participant will have the opportunity to have an 1 hour one-to-one exit interview after having been enrolled in TANGELO for one year. These interviews will provide qualitative insights regarding: 1) the daily life impact of AS for the study participant; 2) any key areas of change over the duration of the study; and 3) the aspects of these changes that are most important.
    - The data from these interviews are not yet analyzed because many participants have not yet completed the entire study.

4. You mentioned that safety was "acceptable" and not the reason for stopping the development of rugonersen, can you comment on what you learned from the safety findings (any side effects etc)?
    - Rugonersen, at the doses and regimens tested in TANGELO, is deemed adequately tolerated. Participants in TANGELO have been monitored for drug and non drug related adverse events.
    - Review of safety data is continuous and ongoing to facilitate the detection of potential safety signals from the study treatment for effective risk assessment and determination of the benefit-risk relationship.
    - Roche is planning to share study results with the scientific and patient community via several channels, including manuscripts and lay patient summaries, in due course and in conjunction with a future external partner.
    - Roche has high quality standards and therefore the safety of the participants in our studies is of utmost importance to us. Particularly when pediatric or other vulnerable populations are involved, we apply extra caution.

5. Your letter stated that "some encouraging effects were observed in the patient's EEG" as compared to natural history data" Why was this not enough to move forward?

- The EEG signal and the observed level of clinical efficacy in TANGELO was insufficient to meet Roche's current internal criteria to move into the next phase of development. However, some elements, including the observed effect on EEG are encouraging, therefore we are looking to find a suitable external partner to further explore the potential of the molecule.
- When deciding whether or not a molecule can transition to the next phase of development, we consider not only the data about PD biomarkers (EEG), efficacy and safety of a given molecule, but also other broad internal and external influences at a given time.

6. Do you think the Bayley is a bad endpoint? Should it still be used in trials of individuals with AS?
    - We believe that the Bayley is generally a good and useful clinical outcome assessment instrument. The Bayley captures changes in individuals with AS with age and can distinguish among different AS genotypes.
    - We recognize there are likely limitations of the Bayley in capturing clinical changes in some domains in AS. Scales specifically developed for AS could be superior and more sensitive to detect changes.

7. Families have reported that they were told they will be able to stay on rugonersen and continue on an extension until sometime early next year. Can you explain the rationale for this and why February 2024?
    - Roche plans to continue the currently running TANGELO long-term extension until February 2024 with a follow up visit up to May 2024. Roche wants to give the chance for families enrolled in TANGELO to continue to receive the drug until February 2024 if they wish to stay enrolled.
    - While TANGELO is still ongoing, our priority is to find a suitable partner to take over the program. Our intention is to support any future transition to a potential partner as much as possible.

8. Are you continuing to collect outcome data on patients through February 2024? Can you tell us which ones?
    - To reduce the burden on participants, the exploratory use of the sleep diary, seizure diary, sleep mat, and polysomnography/home electroencephalogram (PSG/home EEG) has been suspended.
    - The in-clinic EEG is maintained to collect further data
    - The rest of the scales will continue to be administered as per protocol schedule of assessment.
    - In agreement with the Health Authorities, the MRI (Magnetic Resonance Imaging) scan and other assessments will be reduced or removed from the TANGELO schedule of assessment. This will help reduce the burden for participants and their caregivers. The safety of our TANGELO participants remains crucial and Roche will continue to monitor and collect data coming from different safety assessments as part of the TANGELO study.

9. When will you specifically share the study data with the community? Over 70 individuals spent time, money, took time off work, and took a risk with the highest of hopes for their loved ones, and we thank them deeply for what everyone can learn from this. This data, either negative or positive, is for naught if our community and others that remain in the space can't learn from it. As 2 advocacy organizations, representing this community, we need to ensure that this data is shared with ALL. What are you doing to ensure that happens? Will you share the data with the LADDER database?
    - We understand the value of this dataset for the community and we are very grateful to all 62 families who have participated in the study
    - At this time, Roche will share the baseline TANGELO data with the LADDER database.
    - We have already shared the TANGELO results with the PIs and doctors in the trial under confidentiality.
    - As TANGELO is ongoing and while we are looking for a partner it would be premature to share the full dataset at this time.
    - Roche is planning to share study results with the scientific and patient community via several channels, including manuscripts and lay patient summaries, in due course and in conjunction with a future external partner.

10. When will you share data on the half-life of rugonersen with the other companies so we know how long the washout period should be before going on another treatment? Please share now openly if you can.
    - Currently the wash-out period we would recommend before entering into another trial would be 9.5 months.

11. Will you be collecting any data on patients as they go off rugonersen to study the effect of withdrawing from the drug?
    - While we cannot speak on behalf of a potential future partner, Roche is planning to continue to provide study drug in the TANGELO study until Feb 2024. The protocol foresees a 3-month safety follow-up after the last dose, and therefore the study would remain open until May 2024.
    - During that time all adverse events, including those that would be caused by withdrawal effects will be captured.

12. What happens to the data from this study? Will it be provided to each family individually? Are you planning to present the findings at meetings? Publications? Timing?

    - Roche is planning to share study results with the scientific and patient community via several channels, including manuscripts and lay patient summaries, in due course and in conjunction with a future external partner.

13. When can we expect, at a minimum baseline data, to be available to the community?

- We are committed to share data as much as possible and thus Roche will share the baseline TANGELO data with the LADDER database shortly.

14. Some families and PIs found out about the stopping of the clinical trial via the community letter on social media even though it was made very clear to both organizations (FAST/ASF) that the PIs had communicated this information to patients before this letter was shared. This has created a tremendous amount of concern about the way in which these types of communications are rolled out. Can you please comment on this?

    - We are committed to transparent and honest communication. We worked with ASF and FAST to ensure that accurate and complete information was available to the community during the days when our Investigators were in the process of informing families enrolled in the trial.
    - Under regulatory health authority guidelines, Sponsors are not allowed to directly communicate with families enrolled in a clinical trial.
    - While the investigators were in the process of informing trial participants, we were informed that the news started to spread and trial participants may receive the news through other channels, which comes with the risk of sharing incomplete or misleading information. Therefore, it was important to share the correct information with all the facts with transparency with the community as soon as possible.

15. If no one purchases this ASO program from you, but families that feel they are seeing a great response want to remain on the drug, will you be willing to allow any of the PIs to open an academic sponsored IND to continue therapy until another ASO is approved so that these individuals are not lost while waiting, what could be a few more years?
    - We are fully committed to the families enrolled in our clinical trials and care about their well-being. We understand the importance of this matter. At this point the focus is on finding an appropriate partner who can continue the development of rugonersen. While we give this process full priority, Roche will evaluate options for different future scenarios.

16. Someone asked, considering there is a chance that an ASO could be more effective in UPD/ICD genotype, before you stop the program why not try it in those individuals as they could show you the benefit you are looking for?
    - Potential differences in safety and efficacy in UPD/ICD patients compared to deletion and mutation patients is a complex question. We will pass this question on to the future partner.