Community Conversations: Astellas Gene Therapies Webinar Feb 11, 2023

Post-Webinar Additional Q&A provided by Astellas Gene Therapies

1. **Do you foresee resuming trial with the same AT132 product changing protocol or changing inclusion, or developing a novel compound?**
   We are currently working internally and with Regulatory Authorities to determine the best path forward.

2. **What is the approximate investment Astellas has made in AT132?**
   This information is not currently available.

3. **What is the ethical argument for (and against – I'd like to hear both sides of the argument) withholding a drug/pausing a study, that has shown significant benefit to the majority of the patients, when the disease results in no survival? For example, by delaying, you are seeing more deaths by maintaining the status quo than if you were to dose the population with the current results.**
   Investigational drugs are assessed for safety at the individual subject level and there are many levels to ensuring the safety of subjects in a clinical trial; therefore, it is not just one entity who is responsible for pausing or withholding a drug within a trial. The following stakeholders are responsible for ensuring safety of each study subject:

   1. The Regulatory Agency's (FDA) primary objective is to assure safety and the rights of the subjects and to ensure evaluation of the drugs effectiveness.

   2. Sponsors are required to assess and report on the safety of the subjects within the clinical investigation under the law (21 CFR 312); serious safety events can lead the Regulatory Agency to place the study on hold to better understand the risks.

   3. The Investigator (Doctor) commits to protect the safety, rights, and welfare of their subjects within the study.

   4. The investigational site's IRB (investigational review board – also known as independent ethic committee) are also required to protect the safety and welfare of the subjects within the study.

   5. Patient – assesses the risks by reviewing the informed consent form and speaking with their clinical investigator.

   All stakeholders must agree that the potential benefits outweigh the risks to the individual subjects being treated with the investigational drug.

4. **What learnings would you take from the work done so far to future studies around communication and transparency to the overall MTM community?**
   Communication and transparency is an ongoing journey with the MTM community and we are committed to having ongoing dialogues. At the same time, we are taking into account local regulations that may prevent us in sharing information from investigational programs in certain

countries, for example, in Europe. One of the learnings along this process relates to setting expectations and finding a common understanding about the drug development process and its limitations.

5. **Are the dosed children able to speak and eat? (so how are the face muscles and swallow muscles affected?)**
   While we have not formally performed these analyses, we have reports from caregivers from speech and swallowing questionnaires that some children who were dosed have the ability to speak, jabber loudly, and/or alert a caregiver from another room. Caregivers have reported that after dosing, some children have ceased using their G-tube for feeding, while others have continued to use it all yhor some of the time. Some parents have reported an improvement in secretions severity post-dosing.

6. **The issue with kidneys was touched, it was more medical than I know, can there be more information given there please.**
   Thrombotic microangiopathy or TMA has been reported on other AAV gene therapy programs and can lead to kidney problems (Horton RH et al. J Neurol Neurosurg Psychiatry, 2022). Kidney issues and TMA were not seen in the ASPIRO study.

7. **Do you expect/suspect national trial (France, Germany, USA) boards to accept FDA advised changes to the current protocol? Or would Astellas have to open a 'new' clinical trial after the clinical hold?**
   Modifications to the clinical program are part of a large number of ongoing activities within the AT132 program. We are under discussion internally as well as with the Regulatory Authorities to determine the best path forward.

8. **In the past, you have already changed the protocol (for the higher dose control patient-dosed patient duos f.e.), would this 2nd change (what it might be) be too much to accept for the regulatory boards?**
   We are under discussion internally as well as with the Regulatory Authorities to determine the best path forward.

9. **If the lower dose seems to be providing better outcomes, will you still consider the higher dose when the trial resumes?**
   We are under discussion internally as well as with the Regulatory Authorities to determine the best path forward.

10. **Might there be anything in the works for adult females with MTM?**
    Our initial focus is for the treatment of male children with XLMTM. We are open to learning more about the unmet needs from the MTM-CNM community.