AUDENTES THERAPEUTICS

August 7, 2018

Dear XLMTM Community,

Last year, the ASPIRO clinical trial began to study an investigational gene therapy product in boys affected by X-Linked Myotubular Myopathy (XLMTM) . Preliminary findings from the ASPIRO trial were shared earlier this year, and, today, additional interim data and program updates were shared in a press release.

We are sharing this letter as part of our commitment to ongoing, open communication with the XLMTM patient community. Because of the considerable interest in the early findings from the ASPIRO study, we recognize the need for clarity regarding information as it becomes publicly available. Therefore, we wanted to answer some questions you may have and provide context to the press release issued today (also found at www.audentestx.com under investors/press releases).

What are the goals of the ASPIRO investigational gene therapy clinical trial?

- To learn about the safety of the investigational gene therapy product (AT132)
- To learn whether the AT132 gene therapy is effective for the long-term production of myotubularin, the missing or defective protein in XLMTM
- To determine the appropriate amount, or dose, of the investigational gene therapy product AT132

How many participants have been dosed in the clinical trial to date?

- Six (6) participants have been dosed with AT132
- One (1) participant has been randomized to the delayed-treatment control arm of the clinical trial, meaning that he will receive a to be determined dose of AT132 later in the clinical trial
- To date, all dosed participants have been given the first dose level being assessed in the clinical trial
- Today, it was announced that the next dose level will be administered to the next group of participants

What is the significance of the decision to move to the next dose?

- One of the main objectives of ASPIRO is to determine the optimal (most safe and effective) amount (or dose) of AT132
- Escalating the dose in line with the planned protocol is the next step to determine the optimal dose

How did we come to the decision to move to the next dose?

- Audentes confers with an independent Data Monitoring Committee (DMC) to determine whether or not it is advisable to proceed with dose escalation as planned in the study protocol. The protocol is a document that describes the study and how it will be run, which every doctor who is part of the study follows

What is a DMC?

- A DMC is an independent group of experts who monitor patient safety, treatment efficacy and study conduct while a clinical trial is ongoing
- DMC members are selected based on their deep expertise, understanding of clinical trial methodology, patient focus and ability to make sensible recommendations in a rational and consensus driven manner based on data and medical judgment
- The DMC is primarily responsible for assuring the safety and interests of study participants, while assessing the potential clinical activities and monitoring the conduct of the study. Some of their recommendations might relate to:
    - Expanding a dose cohort
    - Opening up a higher dose cohort
    - Safety matters
    - Quality and conduct of the study

What do we consider when deciding whether or not to go to the next dose?

- There are many factors that are weighed when determining whether to escalate the dose:*
  - Safety & efficacy data from previous dose cohorts (in this case, the first dose cohort)
  - Data from preclinical studies
  - The potential for additional benefit or harm
- It is important to stagger the enrollment and dosing of individuals within each new cohort to monitor for adverse events prior to treating additional participants

**Source:*
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf

What are the early, interim findings in the clinical trial?

It is important to note:

- We cannot make any conclusions about the findings of the clinical trial until all subjects are dosed and evaluated for the duration of the study, and the full scope of data is collected and analyzed
- Once the study has completed and data has been analyzed, more complete information about the safety and efficacy of this investigational gene therapy product will become available to the community

Safety Findings Since the Last Interim Data Update in May 2018:

- There were no new treatment-related serious adverse events

Preliminary Efficacy Findings to Date:

- In May 2018, data was shared on week-24 assessments for Patients 1, 2, and 4 (untreated control) as well as earlier assessments for Patients 5, 6, and 7 from the Cohort 1 expansion group. Today, data was shared for Patient 3 at week 24, which included:
  - Increase in CHOP-INTEND neuromuscular function scores
  - Decrease in ventilation requirements
  - Increase in respiratory pressure measures

Muscle Biopsy Findings to Date:

- Muscle biopsies performed in (3) participants at baseline and at week 24 show improvement, specifically they show evidence of:
  - Efficient tissue transduction, or transfer of genetic material, of the investigational gene therapy product. This is measured by the vector copy number (VCN), or the average number of vector genomes (DNA) in each muscle cell nucleus
  - Myotubularin protein levels near or above normal levels in all three patients as measured by a test called the Western Blot
  - Histological improvement (structure and composition of the muscle tissue), as assessed by the size of the myofibers, the location of nuclei and the localization of intra-cellular organelles

It is important to understand that regulatory agencies have not approved the Audentes investigational gene therapy product as safe or effective, as it is still undergoing formal assessment in clinical trials. The investigational gene therapy product is not approved for commercial sale and is only being used in clinical trial settings.

What is the significance of the muscle biopsy data?

- A muscle biopsy is often used to diagnose XLMTM. The biopsy shows the unique histopathology (changes in tissues observed by a microscope) characterized by the disease
- In ASPIRO, a muscle biopsy is taken from a participant at baseline (before receiving the investigational product) and again 24 and 48 weeks following administration
- The muscle biopsy helps us to better understand whether the underlying pathology (changes in muscle tissue) is improving in participants who have received AT132. Muscle biopsies also provide information on how well the study drug gets to the muscle cells and produces myotubularin

When will the next release of findings from the ASPIRO clinical trial take place?

- The next planned release of additional data will take place later in 2018 at the 23rd International Congress of the World Muscle Society, October 2–6, 2018

Where can general information about the clinical trial design be found?

- USA: Visit ClinicalTrials.gov and enter the term "ASPIRO"
    - https://clinicaltrials.gov/ct2/show/NCT03199469?term=aspiro&rank=1
- Europe: Visit EU Clinical Trials Register at www.clinicaltrialsregister.eu
    - Please note we anticipate the clinical trial will be listed shortly

We would like to ask for your continued partnership in helping the XLMTM community understand the need to refrain from any discussions (including social media, and other online or offline communications) about how the children in ASPIRO may be doing while the clinical trial is in progress. This includes a sincere request to the XLMTM patient community to please refrain from proactively asking parents of children enrolled in ASPIRO for information regarding their child's medical status during the conduct of the study. This is critical in helping to maintain the integrity of the data coming out of the trial. Our hope is to demonstrate the safety and efficacy of this gene therapy product such that it will benefit children and families affected by XLMTM in the shortest time possible. We do this best by running a robustly controlled and scientifically disciplined clinical trial and we need your help in making sure this occurs.

We hope this information is helpful in answering some of the questions you may have.

- If parents of children in the clinical trial have questions, we suggest they directly contact their clinical trial doctor and staff with questions
- For general inquiries, Patient Advocacy at Audentes Therapeutics can be contacted at: patientadvocacy@audentestx.com

Again, this investigational gene therapy product is not approved by regulatory agencies as safe or effective and it will continue to undergo formal assessment in the clinical trial. We look forward to sharing further information at a suitable time point.

Sincerely,

Suyash Prasad MD, Pediatrician, Senior Vice President and Chief Medical Officer

Glossary of Terms

Adverse Event (AE):
Any undesirable experience/medical occurrence associated with use of an investigational product. Participants in clinical trials report these to the clinical trial physician. The physician and staff will determine if it is related to the use of the investigational product.

CHOP-INTEND:
An assessment tool used to measure neuromuscular function, including motor skills. CHOP-INTEND stands for, "**C**hildren's **H**ospital of **P**hiladelphia **IN**fant **TE**st of **N**euromuscular **D**isorders."

Cohort:
A group of participants in a clinical trial, who are similar and observed over the same period of time. They may be similar in terms of age, dose given, clinical symptoms, or other defined characteristics. In ASPIRO, cohorts are similar in terms of the dose received.

DMC (Data Monitoring Committee):
A Data Monitoring Committee (DMC) is an independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing.

Dose Escalation:
A progressive increase in the anount of treatment given, in order to understand better the safety and efficacy profile

Histology:
The study of the structure, composition and function of cells, tissues and organs.

Histopathology:
The study of changes in tissues caused by a disease.

Interim:
Early, incomplete in this context, part way through the study

MIP:
Maximal inspiratory pressure, or the greatest amount of pressure one can create while inhaling a breath.

MEP:
Maximal expiratory pressure, or the greatest amount of pressure one can create while exhaling a breath.

Myofiber:
Part of a single muscle cell.

Myotubularin:
The protein that is limited or absent in the muscles of those with X-Linked Myotubular Myopathy.

Protein expression:
The way in which proteins are synthesized, modified and regulated in the body.

Glossary of Terms (continued)

Serious Adverse Event (SAE):
Any type of an adverse event which: results in death, is life threatening/poses the risk of death, requires hospitalization, causes persistent of significant disability/incapacity, results in birth defects, or another conditions which clinical trial physicians determine represents significant hazards.

- More information may be found at: http://www.hhs.gov/ohrp/policy/advevntguid.html.

Study Protocol:
A document that describes the objectives, design, methodology, statistical considerations and aspects related to a clinical trial. Study protocols must meet standards that adhere to the principles of Good Clinical Practice, and are used to obtain ethics approval by local Ethics Committees or Institutional Review Boards.

Systemic administration:
A route of administration of a substance into the circulatory system so that the entire body is affected.

Transduction:
The transfer of genetic material from one cell to another by means of a virus.

Vector copy number:
The average number of vector genomes (DNA) in each muscle cell nucleus.

Western Blot:
A test that is conducted to identify and quantify a specific protein from a complex mixture of proteins extracted from cells.