

October 5, 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 Phase 1/2 ASPIRO trial were shared earlier this year, and, today, additional interim data and program updates were shared with healthcare providers at a major medical and scientific conference, the 23<sup>rd</sup> International Congress of the World Muscle Society, which was held in Mendoza, Argentina.

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](http://www.audentestx.com) under investors/press releases).

**What are the goals of the Phase 1/2 ASPIRO investigational gene therapy clinical trial?**

- To learn about the safety of the investigational gene therapy product (AT132)
- To learn whether the investigational 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

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

- Eight (8) participants have been enrolled in ASPIRO to date
  - Seven (7) participants have been dosed with the investigational gene therapy product
    - Six (6) participants have been given the first dose level in Cohort 1
    - One (1) participant has been given the second dose level in Cohort 2
  - One (1) participant has been randomized to the delayed-treatment control arm of the clinical trial, meaning that he will receive the optimal dose (which is yet to be determined) of the investigational gene therapy later in the clinical trial
- Enrollment of the remaining three (3) participants in Cohort 2 is expected to commence in the coming weeks
  - One (1) of the three (3) remaining participants in Cohort 2 will be randomized to the delayed-treatment control arm of the clinical trial

**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 August 2018:*

Ongoing safety assessments are critical to proper determination of potential safety issues and adverse events.

- There have been no new treatment-related serious adverse events since the interim update given in May 2018 at the American Society of Gene and Cell Therapies (ASGCT), including from the August 2018 interim update

*Preliminary Efficacy Findings Since the Last Interim Data Update in August 2018:*

- Today, incremental data were shared for all participants, including week-48 data in the earliest treated participants and week-4 results from the first participant in Cohort 2 who was given the second dose level
- Preliminary efficacy findings in all treated participants included:
  - Increase in CHOP INTEND neuromuscular function scores
  - Increase in respiratory pressure measures as demonstrated by gains in maximal inspiratory pressure (MIP), a measure of respiratory muscle strength
  - Decrease in ventilation requirements

*Muscle Biopsy Findings Since the Last Interim Data Update in August 2018:*

- Today, data were shared on muscle biopsies performed in (1) additional participant at baseline and week-24
  - Data from three (3) participants were shared in the August 2018 interim update
  - Week-24 biopsy results in all treated participants show:
    - 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 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 CHOP INTEND scale?**

- The CHOP INTEND scale measures key motor function developmental milestones that children would typically have within the first year of life including rolling over, head control and sitting unassisted (for more than 5 seconds)

**What is the significance of the muscle biopsy data?**

- 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 the investigational gene therapy
- 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?**

- Audentes typically provides updates at leading scientific conferences. While we do not have an exact date for the next release, we do plan to keep the patient and scientific community updated on ASPIRO progress as appropriate through press releases, hosted conference calls and scientific forums.

**Is the ASPIRO clinical trial still enrolling?**

- All participants currently needed to enroll the ASPIRO study have been identified in INCEPTUS

**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](http://www.clinicaltrialsregister.eu) and enter the term "ASPIRO"
  - <https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000876-27/DE>

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](mailto: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, "Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders."

### **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 amount 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.

### **Phase 1/2:**

A phase 1/2 clinical trial is a study that tests the safety, efficacy and optimal dose of a potential new treatment all at once, as opposed to separating the goals into multiple phases. Phase 1/2 clinical trials are common in rare conditions due to the small population size.

### **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 or 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.