

August 26, 2019

Dear Patient Leaders of the XLMTM Community,

In September 2017, the Phase 1/2 ASPIRO investigational gene therapy clinical trial began to study an investigational gene therapy product candidate in boys affected by X-Linked Myotubular Myopathy (XLMTM). On August 6, 2019 Audentes shared additional information about the clinical trial in a press release, which can be found in the Investors + Media section of our website at [www.audentestx.com](http://www.audentestx.com).

We are sharing this letter as part of our commitment to ongoing, open communication with patient leaders of the XLMTM patient community. Because of the considerable interest in 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.

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 candidate
- To determine the appropriate amount, or optimal dose, of the investigational gene therapy product candidate
- To learn whether the investigational gene therapy product candidate is effective for the production of myotubularin, the missing or defective protein in XLMTM

It is important to note:

- We cannot make any firm conclusions about the findings of the clinical trial until all subjects are dosed and evaluated for the duration of the clinical trial, and the full scope of data is collected and analyzed

It is important to understand that regulatory agencies have not approved the Audentes investigational gene therapy product candidate or determined that it is 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 available in clinical trial settings.

What are the next steps for the Phase 1/2 ASPIRO investigational gene therapy clinical trial?

- The ASPIRO clinical trial is ongoing with sites activated in the United States, Canada and Europe
- We have selected  $3 \times 10^{14}$  vg/kg as the optimal dose in the ASPIRO clinical trial
- Following interactions with the FDA and EMA, we have decided to enroll eight additional XLMTM patients into the ASPIRO clinical trial pivotal expansion cohort, designed to further evaluate the safety and efficacy profile of the investigational gene therapy product candidate at a dose of  $3 \times 10^{14}$  vg/kg
- The eight patients who will be enrolled in the pivotal expansion cohort will include four age-matched pairs who are within six months of age. One patient from each pair will be randomized to receive a dose of the investigational gene therapy product and one will be selected as a delayed treatment control. The delayed treatment control patients will receive a dose of the investigational gene therapy product after 24 weeks of data is collected on all patients who previously received a dose in the pivotal expansion cohort. Enrollment of eight additional participants in the pivotal expansion cohort is expected to be completed in the fall of 2019

What changes were made to the inclusion criteria and primary efficacy endpoint in the pivotal cohort?

- The inclusion criteria for age remains the same: less than 5 years of age or have been enrolled in INCEPTUS, the pre-phase 1 non-interventional clinical assessment study
- Two updates were made on inclusion criteria for enrollment into the pivotal cohort:
  1. Patients must be on invasive ventilator support for 20-24 hours per day
  2. Patients must be unable to sit without assistance for at least 30 seconds
- The primary efficacy endpoint in the pivotal cohort is defined as change from baseline in hours of ventilatory support over time through week 24

What are all the cohorts currently in the Phase 1/2 ASPIRO investigational gene therapy clinical trial?

- Cohort 1 (dose is  $1 \times 10^{14}$  vg/kg)
- Cohort 2 (dose is  $3 \times 10^{14}$  vg/kg)
- Pivotal Expansion Cohort (dose is  $3 \times 10^{14}$  vg/kg)

Is the Phase 1/2 ASPIRO investigational gene therapy clinical trial still enrolling?

- Yes, ASPIRO is currently enrolling patients for the pivotal expansion cohort, however, all participants intended to be dosed have been identified
- Each clinical trial site maintains a wait-list which they manage for patients interested in participating in the clinical trials. These sites continue to evaluate patients on these wait-lists based on the protocol criteria and in case there is a future need to enroll more patients into ASPIRO
- In addition to the inclusion/exclusion criteria listed on [clinicaltrials.gov](http://clinicaltrials.gov), each clinical trial site may have additional considerations, such as capacity at their site. The overall number of patients in the clinical trial is also limited.

What is the timing for submissions to regulatory agencies?

- We plan to submit the following:
  - BLA (Biologics License Application) in mid-2020 to the FDA in the United States
  - MAA (Marketing Authorisation Application) in the second half of 2020 to the EMA in Europe

What are the plans for conducting clinical trials in patients older than 5 years of age?

- Since we first began interacting with the XLMTM community years ago, it has been clear that treatment for older children is a significant need
- We are working on how to help the broadest population gain access (if approved by regulators), including considering whether additional studies may help expand potential future access for older patients
- At this time, we do not know what age range regulators may approve for use

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

- The next clinical data presentation is planned to take place at the 24th International Annual Congress of the World Muscle Society (WMS) in Copenhagen, Denmark, October 1-5, 2019

What is the status of the INCEPTUS clinical trial?

- INCEPTUS, the pre-phase 1 non-interventional clinical assessment trial, is currently closed for enrollment and will likely remain closed for the time being as we continue to gather ongoing longitudinal data on the children currently in the clinical assessment trial.

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 understanding the need to refrain from any discussions (including social media, media, online, telephone or in-person communications) about how children in the ASPIRO clinical trial may be doing while the trial is in progress. Please refrain from proactively asking parents of children enrolled in the ASPIRO clinical trial for information regarding their child’s medical status. This is critical in helping to maintain the integrity of the data coming out of the clinical trial.

Our hope is to demonstrate the safety and efficacy profile of the investigational gene therapy product candidate to meet the needs of the regulators, such that it will benefit as many children and families affected by XLMTM as possible, in the shortest amount of time. 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.

- Parents or caregivers of a child enrolled in the ASPIRO clinical trial should direct all questions to the clinical trial doctor or his/her staff
- For general inquiries, please contact Patient Advocacy at Audentes at: [patientadvocacy@audentestx.com](mailto:patientadvocacy@audentestx.com)

Sincerely,

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