AUDENTES

AT132 Gene Therapy for XLMTM – Commonly Asked Questions & Answers

1. What is AT132 and what is the aim of its clinical development program?

The Audentes gene therapy product candidate to treat XLMTM is called AT132. The overall aim of the clinical development program is to evaluate whether AT132 is safe and effective in XLMTM, and to get the drug approved quickly in order to benefit patients with XLMTM as rapidly as possible. Audentes will collect the necessary data in clinical studies and then, if the outcomes from the clinical studies are positive, file an application for potential approval to sell AT132 commercially with regulatory agencies around the world (e.g. U.S. Food and Drug Administration, or FDA, and the European Medicines Agency, or EMA).

2. What is INCEPTUS? What is ASPIRO?

Both INCEPTUS and ASPIRO are clinical studies that are, or are planned to be, conducted by Audentes Therapeutics. INCEPTUS and ASPIRO form part of the clinical development program for AT132.

- INCEPTUS (which means "begun" or "beginning" in Latin) is a non-interventional (i.e. no gene therapy with AT132 administered), prospective study to evaluate male XLMTM patients less than 4 years of age (i.e. 3 years or younger). The goal of INCEPTUS is to determine which assessments, or tests, best identify the key characteristics of the disease, and to serve as a longitudinal baseline and within patient control for ASPIRO. INCEPTUS is also designed to facilitate certain operational aspects for subjects who enroll in ASPIRO.
- ASPIRO (which means "to aspire" in Latin) is the first clinical study of gene therapy with AT132 for male XLMTM patients less than 5 years of age (i.e. 4 years or younger). The goal of ASPIRO is to determine if AT132 is safe to administer and has a beneficial effect on the signs and symptoms of XLMTM.

3. Why is there a difference in the ages of patients being enrolled into INCEPTUS vs. ASPIRO and what happens if my child enrolls in INCEPTUS but is too old to participate in ASPIRO?

Patients must be less than 5 years of age (i.e. 4 years or younger) to be included in ASPIRO and have participated in INCEPTUS. Since INCEPTUS began enrolling in 2016 and ASPIRO is planned to not begin enrolling patients until later in 2017, the lower age limit was set in INCEPTUS so that patients are less likely to become ineligible for ASPIRO because of their age.

4. When will the INCEPTUS study begin to enroll patients? When will the ASPIRO study begin to enroll patients?

- The INCEPTUS study has almost completed patient enrollment. All patients have been identified and no more patients are being recruited. Information on the participating study centers is available on the clinicaltrials.gov website.
- The ASPIRO study is expected to begin enrolling patients in the latter half of 2017. The exact timing will depend on continued approvals of the study by various regulatory agencies (e.g. Health Canada in Canada, MHRA in the UK, PEI in Germany, ANSM in France, etc), Ethics Committees, Institutional Review Boards and other review committees (such as the U.S. Recombinant DNA Advisory Committee).

5. How many patients will be enrolled in INCEPTUS? How many patients will be enrolled in ASPIRO?

- The INCEPTUS study was designed to enroll 12–16 patients who meet the inclusion criteria.
- The ASPIRO study is planned to enroll approximately 12 patients who meet inclusion criteria.

6. What are the inclusion criteria for INCEPTUS?

a. Male patients
b. 3 years or younger (less than 4 years old)
c. Diagnosis of XLMTM resulting from a confirmed mutation in the MTM1 gene
d. Mechanical ventilatory support required (e.g. ranging from 24 hours per day full-time mechanical ventilation, to noninvasive support such as continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP] during sleeping hours)
e. Access to medical records
f. Signed informed consent by the parent(s) or legally authorized representative(s)
g. Patient and parent(s) or legally authorized representative(s) are willing and able to comply with study visits and study procedures

7. What assessments are being conducted in INCEPTUS? How many days and visits are required?

There are a series of assessments that will be conducted over 2 days every 3 months for up to 2 years. The assessments cover safety (ECG, blood draws, physical exam, height/weight, X-ray, etc), physical and movement assessments, respiratory (breathing) measurements, and questionnaires to evaluate respiratory status and quality of life. These assessments are important in helping establish an adequate baseline of the disease in preparation for ASPIRO.

8. What costs are covered for study visits for INCEPTUS?

Audentes will cover the costs of patient and family travel to/from the study site. These costs may include airfare, buses, trains, taxis, meals (daily stipend per person), and hotels for the patient, two parents, siblings, and a caregiver.

9. Does enrollment in INCEPTUS guarantee a patient's participation in ASPIRO?

No. There are additional inclusion criteria (for example antibody titer levels) for ASPIRO, which must be met before a patient can be enrolled in the ASPIRO study. Additionally, if a patient has certain concurrent illnesses, such as an infection, they will not be able to enter ASPIRO until they have recovered. The intent and hope is for the majority of patients in INCEPTUS to be enrolled into ASPIRO.

10. Does a patient have to be enrolled in INCEPTUS to be enrolled in ASPIRO?

No. However, as INCEPTUS patients will already be familiar to the doctors at the study site, and data from INCEPTUS patients will have been collected for establishing a patient's baseline disease status, it is planned to give INCEPTUS patients priority for enrollment into ASPIRO.

11. If a patient is enrolled in INCEPTUS, are they obliged to enroll in ASPIRO?

No. Participation in INCEPTUS does not oblige a patient to participate in ASPIRO, nor does it guarantee enrollment in ASPIRO. The studies are independent from each other and require separate approval from regulatory agencies in relevant countries, and then from Institutional Review Boards and ethics committees at specific trial sites. Each study also requires separate consent from the patients' parents (or their legally authorized representatives). However, the hope is that patients participating in INCEPTUS will agree to participate in ASPIRO (assuming that their doctors determine they meet the eligibility criteria), as this makes the data from before and after treatment easier to interpret and understand.

12. If there are 12–16 patients in INCEPTUS and 12 in ASPIRO, how will it be decided which patients enroll in ASPIRO?

Enrollment into ASPIRO will depend upon when each clinical study site has the appropriate Institutional Review Board or Ethics Committee approval in place. Once a site is approved for enrolling patients into ASPIRO, the doctor at the site will work with each of their INCEPTUS patients to determine whether they meet the eligibility criteria for ASPIRO, and if so, when they might be able to enroll. Each of the clinical trial sites will maintain a back-up list of patients who could potentially be enrolled if the number of patients in the ASPIRO study is expanded based on the results seen and/or at the request of regulators. The choice of which patients to include is determined solely by the doctors at the trial sites in discussion with the patients' families. Neither Audentes nor any other members of the MTM community have any input into the choice of which patients will participate in ASPIRO.

13. What is the design of the ASPIRO study?

The ASPIRO study is a phase 1/2 multicenter, multinational, open-label, ascending dose, delayed-treatment concurrent control clinical study in 12 patients. The study is planned to be conducted in approximately 8 study centers in the United States, Canada, the United Kingdom, France, and Germany. Patients will be randomly assigned to one of two arms. They will either receive a single dose of AT132 once they complete a screening period or they will be assigned to

the delayed-treatment control arm of the study. Patients who are assigned to the delayed-treatment control arm will still receive AT132 (there is no placebo in this study), but, for these patients, dosing will not take place until the optimal dose is selected. Selection of the optimal dose is expected to take between 6 and 12 months after the first patient has been dosed. Open-label means that there is no blinding; patients and doctors will know what dose of AT132 they are receiving or whether they are in the control arm.

- Nine patients will be randomly assigned to the AT132 treatment arm (3 patients in each dose cohort) and 3 patients will be assigned to the delayed-treatment control arm (1 patient in each dose cohort).
- Each dosing level is referred to as a cohort, and each patient receives only one dose of AT132, according to the cohort that they are assigned to. There will be up to three different dose cohorts. The first cohort will receive the initial dose. If there are no safety concerns, the second cohort will receive the mid-level dose, and the third cohort will receive the highest dose. It is important to realize that dose cohort 1 (initial dose) is expected to, based on pre-clinical data, deliver therapeutic benefit.
- Once the optimal dose is selected (after the different dose levels have been tested and following conversations with the regulatory authorities), the delayed-treatment control patients will be treated with this optimal dose.
- Patients who are assigned to the delayed-treatment control arm of the study will undergo many of the same tests and procedures (such as physical therapy and breathing assessments) as the patients treated with AT132. However, in order to minimize the burden on these patients, their study visits will be less frequent, and some assessments (for example, muscle biopsies) will be excluded altogether until the patient receives AT132.

All patients in the ASPIRO study will receive a single dose of AT132 unless there is some unforeseen safety issue that prevents further dosing of patients in the study.

14. Why does the ASPIRO study include a control patient within each cohort?

The study has been designed to include one delayed-treatment concurrent control patient per cohort. The control patient will receive treatment with AT132, but not until the optimal dose has been identified after treating all three dose cohorts. The purpose of including control patients in the ASPIRO study is to help determine the benefits and risks of AT132 by comparing patients who receive treatment to control patients who receive no treatment (for a period of time). Clinical trials that include control patients are considered to be more scientifically robust. It is Audentes' hope that by designing and conducting a scientifically robust clinical trial, the development and approval process will move as quickly as possible so that all patients may have access to AT132 sooner.

It is important to realize that the delayed-treatment control patients (who will be determined by chance – a process known as randomization) will only act as controls for a temporary period, and will receive gene therapy after the initial comparison period is over. In order to limit the burden during this period, control patients will have fewer study visits and procedures until they receive AT132. Ultimately all patients in the ASPIRO study will receive gene therapy with

AT132. Although three children (one in each cohort) will receive gene therapy at a date later than the other patients in each cohort, the benefit for these children is that much more will be known about the effects of gene therapy by this time. In particular, we hope to have identified the most appropriate dose by the time we administer AT132 to the control subjects.

15. Will there be other clinical study opportunities for the INCEPTUS patients who don't qualify for ASPIRO or other XLMTM patients not enrolled in ASPIRO?

Although there will initially be 12 patients enrolled in ASPIRO, if results from this initial study are positive, it may be possible to enroll patients into additional studies that are suggested or required by regulatory agencies. Audentes does not currently have plans to conduct any additional studies beyond ASPIRO, and any plans to enroll beyond the currently planned 12 patients in ASPIRO will need to be discussed with and approved by regulatory agencies in the appropriate region (e.g. FDA in the United States, MHRA in the UK, PEI in Germany, etc).

16. What are the challenges that have hindered earlier initiation of clinical studies?

- Audentes is working as hard and as fast as possible to initiate clinical studies of AT132.
- Gene therapy is a new and a highly innovative approach to treating disease. The manufacture of gene therapy products is very complex. There are a number of regulatory requirements which need to be met in order to confirm that product is of high enough quality, purity and safety to administer to humans, and, in particular, children. In addition, the quantities of product needed for treating neuromuscular diseases such as XLMTM are significant, which means that the manufacturing process has to be 'scaled up' in size in order to conduct clinical studies. This also adds complexity. Due to these challenges, Audentes has invested in a manufacturing facility to produce AT132 for clinical studies.
- There were a number of pre-clinical studies, which have now been completed, that were designed to assess the safety of AT132. These studies were required to be submitted and agreed to by regulatory agencies prior to the conduct of studies in humans.
- Once regulatory agency approval has been granted, the study sites must conduct their site initiation work (ethics committee approval, contract authorization, etc). The FDA has cleared the IND in the US; and the clinical trial applications for the European countries are progressing.
- The aim of the clinical development program (human studies) is to test the safety and efficacy of AT132 for XLMTM in patients, and collect the data necessary to file an application for the marketing approval of AT132 in order to make it available for all patients with XLMTM as rapidly as possible.

17. What is Audentes' role as Sponsor of the INCEPTUS and ASPIRO studies?

Audentes is both the regulatory and the financial Sponsor of the INCEPTUS and ASPIRO studies. This means that Audentes is responsible for designing the clinical program, identifying trial sites, supplying study drug, and conducting

interactions with regulatory agencies (e.g. FDA and EMA). In addition, Audentes has sole financial responsibility for all aspects of the INCEPTUS and ASPIRO studies; no outside funding sources are required in order to be able to initiate, run, and complete these studies.

18. What does 'the FDA has cleared the IND' mean?

Once an IND is submitted, the FDA has 30 days in which to review the application that contains information on the animal studies conducted with AT132, how the product is made and tested, and the clinical trial protocol. IND clearance means that the FDA has deemed that Audentes may proceed with initiating the ASPIRO trial in the United States.

19. Now that the FDA has cleared in the US what are the plans for Europe?

European countries require additional information related to the manufacturing and testing of AT132, in addition to the information submitted to the FDA. This information is being generated now and the clinical trial applications will be submitted to the regulatory agencies in France, Germany and the U.K. in a few months.

20. How does Audentes work with the MTM Patient Advocacy Groups?

Audentes has frequent communications with all of the MTM patient groups. This takes various forms, including emails, one-on-one phone calls, in-person meetings, and regular group discussions with the leaders of each advocacy group. The intent is to provide an open, transparent dialogue between Audentes and the patient community about the status of the clinical development program, and to help address any questions, concerns or issues that patients and their families have about the studies or gene therapy. These discussions do not include any discussion about eligibility of any individual patients for the AT132 clinical development program (including INCEPTUS or ASPIRO) nor any other aspects of individual patients' care.