Phase 3 Study of Ataluren in Patients with Nonsense Mutation Duchenne Muscular Dystrophy

Frequently Asked Questions

What is ataluren?

Ataluren (formerly called PTC124®) is an investigational new drug, which means it is being tested as a potential treatment but has not yet been approved for sale by regulatory authorities in any country.

Ataluren targets a particular type of mutation, or change in the genetic code, known as a nonsense mutation. Nonsense mutations are errors in the genetic code that cause a disorder by prematurely stopping the production of a critical protein, such as the protein dystrophin in the case of Duchenne muscular dystrophy (DMD). Approximately 13 percent of cases of DMD are caused by a nonsense mutation, also known as a premature stop codon. Ataluren has the potential to treat the underlying cause of the disorder by causing the cellular machinery to overcome the nonsense mutation and produce a functioning protein.

What is the purpose and design of the Phase 3 study?

The main goals of the Phase 3 study are to confirm the safety and efficacy of ataluren in nonsense mutation DMD (nmDMD). Efficacy will be determined primarily by measuring changes in walking distance based on the 6-minute walk test. Additional measures of physical function and quality of life will be assessed as well. The study is intended to generate the information required to support approval of ataluren by regulatory authorities in the US and EU.

The Phase 3 study is randomized, double-blinded, and placebo-controlled — participants will be randomly assigned to receive either ataluren or a placebo (a substance that looks and tastes the same as ataluren, but does not actually contain the drug) for 48 weeks. The patient, the patient's family, the study investigators, site staff, and PTC Therapeutics personnel cannot choose the group and, barring exceptional circumstances, will not know which treatment each participant is receiving until after the study is over.

Who is eligible to participate in the Phase 3 study?

Full inclusion and exclusion criteria are available at www.clinicaltrials.gov and will be explained in detail by the physicians conducting the study, but key considerations follow. Potential participants must:

- Have a nonsense mutation, which is determined through a DNA blood test to evaluate the dystrophin gene (genotyping). Parents of patients with DMD who have not had this test should consider discussing it with their doctor or genetic counselor.
- Be between 7 and 16 years old
- Be able to walk at least 150 meters (165 yards) unassisted during a 6-minute walk test but less than a distance, specified in the trial protocol, that would be predicted for boys of the same age and weight (This will be explained more fully at the trial site).
- Have been on stable corticosteroid treatment (i.e., prednisone, prednisolone, or deflazacort) at least 6 months immediately prior to the start of study treatment, with no significant change in dosage (other than for body weight change) or treatment regimen for at least 3 months before enrolling in the trial. The following corticosteroid regimens are permitted: daily, every other day, 10 days on – 10 days off, and weekend (2 consecutive days).
- Show that evidence of DMD based on characteristic symptoms or signs (such as muscle weakness, waddling gait, and Gowers' maneuver, creatine kinase levels and difficulty in walking) was apparent by age 6.

The decision as to whether a patient is appropriate for the study ultimately is made by the principal investigator at the study site who, in communication with the patient and the family, is best able to weigh the potential risks and benefits for each potential participant.

Why is enrollment in the trial limited to participants who are still walking?

The 6-minute walk test is a clinically validated endpoint that has been used in other disorders and is currently considered by regulatory authorities to be the best way to evaluate therapies in DMD. Walking is a key aspect of physical functioning that is easily observed and measured. Over the course of a year it is easier to see a decrease in walking ability than in other functions, which makes it easier to determine the effect of ataluren when compared to placebo. For that reason, a change in walking ability is the primary endpoint, or factor to be measured, in the trial.

Why is seven years the minimum age?

While we believe that all patients with a nonsense mutation could be candidates for ataluren as a therapy, this study needs to focus on patients who are at least 7 years old in order to demonstrate ataluren's ability to improve or maintain ambulation compared to placebo during a 48-week trial. The age is determined based on recently published natural history studies that examine the course of the disorder and have shown that boys with DMD generally improve in their ability to walk until about age 7.

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What does participation in the trial involve?

Before being considered for enrollment in the study and undergoing testing or receiving study medication, a patient and his parent or guardian must be informed about the study by the medical researchers. This requires signing a document called an Informed Consent, indicating a willingness to participate. The Informed Consent explains the trial in great detail to allow families to assess the risks and benefits of participation. Patients may also be asked to sign a less detailed assent form that explains the basics of the trial in age-appropriate language. A copy of each signed form is provided to the patient and family.

After the consent process, the patient will be screened to determine whether he is eligible to participate in the study. These screening procedures will usually be done at a clinic visit during the two-week period before treatment would be scheduled to start. Screening will determine whether a potential participant in the trial meets the study entrance requirements and can contribute data that will help achieve the study goals.

In this study, participants who receive ataluren will be compared to those who do not. The participants will be divided into 2 groups of about 110 patients each. The amount of drug or placebo used is determined by body weight in kilograms (1 kilogram equals 2.2 pounds):

- Group 1 will receive ataluren at a dose of 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening
- Group 2 will receive a placebo (inactive drug powder that looks and tastes the same as ataluren) at a dose of 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening

The drug or placebo is supplied in a packet as granules that have a mild vanilla flavor. It can be mixed with water, milk or certain semi-solid foods.

During the 48 weeks of treatment, a clinic visit will be required every 8 weeks. At these visits, participants will perform the 6-minute walk test, have other tests and evaluations and be asked about their quality of life and changes in activities of daily living. At the end of 48 weeks, it is anticipated that in countries where ataluren is not commercially available participants who complete the trial will have the opportunity to enter into an extension study in which they will receive ataluren. If a participant does not wish to enter the extension study or stops the study early, a short-term follow-up visit will be performed 6 weeks after stopping the drug or placebo to document the general health of the participant.

Where is the Phase 3 trial being conducted and how long will it be accepting patients?

Study sites are planned in Australia, Belgium, Brazil, Canada, Chile, Czech Republic, England, France, Germany, Israel, Italy, Poland, South Korea, Spain, Sweden, Switzerland, Turkey and the United States. All sites will be posted on www.clinicaltrials.gov under NCT01826487 and www.ptcbio.com/ataluren_dmd_trialsites. The study will continue enrolling new patients until the necessary number of participants has been reached. It is estimated that enrollment will be completed by mid-2014. The sooner patients enroll in the study, the faster the study can be completed, and the sooner the results can be known.

How can a patient enroll in the Phase 3 study?

As soon as each site is open to enroll patients, contact details for the site will be listed on www.clinicaltrials.gov under NCT01826487 and www.ptcbio.com/ataluren_dmd_trial. Families can contact a site directly to inquire about study participation.

Is there any cost to participate in the trial?

All costs of physical examinations, screening, laboratory and other tests, as well as the cost of the drug, are covered by PTC Therapeutics. Reimbursement will be made for reasonable costs of travel, meals and lodging necessary for clinic visits, subject to limitations that will be explained at the trial site.

Can ataluren be purchased from other countries?

No. Ataluren is an investigational drug that has not yet been approved for sale anywhere in the world and cannot be legally purchased for use by a patient. The only form of ataluren that meets regulatory requirements for safety and purity and is appropriate for use in humans is manufactured by PTC Therapeutics.

If PTC is granted conditional approval in Europe, why couldn't patients just buy the drug rather than participating in the trial?

The completion of the Phase 3 study is critical to ataluren's full approval in the EU and in the US, and it will also serve as the basis for potential approvals in other countries. The granting of conditional approval in the EU remains uncertain, and even after approval, access to ataluren could take several months due to the processes in each specific country.

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