

Frequently Asked Questions About the Phase 2b DMD/BMD Trial

1. Q: What is PTC124?

A: PTC124 is an investigational new drug, which means it is being tested as a potential treatment but that it has not yet been approved for sale by the U.S. Food and Drug Administration (FDA), the European Medicines Evaluation Agency (EMA), nor by regulatory authorities in any other country. PTC124 targets a particular genetic alteration known as a nonsense mutation. Nonsense mutations are errors in the genetic code that cause a genetic disorder by prematurely stopping the production of a critical protein, such as dystrophin in the case of Duchenne/Becker muscular dystrophy (DMD/BMD). Approximately 10-15 percent of patients with DMD/BMD have the disease due to a nonsense mutation. In such patients, PTC124 has the potential to treat the underlying cause of the disease by causing the cellular machinery to overcome the premature stop signal in the genetic code and produce the dystrophin protein.

2. Q: What is the design and purpose of the Phase 2b DMD/BMD trial?

A: The trial is an international, multicenter, randomized, double-blind, placebo-controlled study that evaluates two different dose levels of the drug. The main goals of the study are to understand whether PTC124 can improve walking, activity, muscle function, and strength and whether the drug can safely be given for a long period. This study is also intended to generate the information required to support approval by the FDA, EMA, and other regulatory authorities.

3. Q: Who can qualify to participate in the Phase 2b DMD/BMD trial?

A: To be considered for this study, patients must have had a DNA blood test to evaluate the dystrophin gene and know that a nonsense mutation is the basis for their DMD/BMD. This test is known as genotyping or full-length gene-sequencing. Patients with DMD/BMD who have not been genotyped should consider discussing gene-sequencing with their treating physician or genetic counselor. Knowing the genetic sequence of a disease-causing gene may prove useful in determining eligibility for clinical trials involving certain types of experimental therapies. Facilities that perform gene-sequencing can be located through the Gene Tests website (www.genetests.org); click "Laboratory Directory" to search for the locations of gene-sequencing facilities.

In addition to having a nonsense mutation, study participants must be at least 5 years of age and be able to walk at least 75 meters (80 yards) unassisted in a 6-minute time period. They must also have exhibited an elevated creatine kinase level in the blood and evidence of DMD/BMD based on the medically documented onset of characteristic clinical symptoms or signs (e.g., muscle weakness, waddling gait, Gowers' maneuver) by 9 years of age. Other inclusion criteria will be explained prior to trial enrollment.

4. Q: Why is enrollment in the Phase 2b DMD/BMD trial limited to participants who are ambulatory and at least 5 years of age?

A: Because the trial is primarily evaluating whether PTC124 will improve walking ability in boys and young men with DMD/BMD, it includes only patients who are still able to walk but have difficulty doing so. This study will compare results in participants randomly assigned to receive PTC124 for 48 weeks to results in participants who are

randomly assigned to receive a placebo (a substance that looks and tastes like PTC124, but does not actually contain the drug) for 48 weeks. During this time, it is necessary to repeatedly evaluate the participants with a scientifically valid test of functioning. For this purpose, a test of walking, called the 6-minute walk test, has been selected. The 6-minute walk test has been used in other clinical trials and is expected to be the best way to demonstrate an improvement in functioning with PTC124. In this test, participants must walk as rapidly and as far as they can for 6 minutes. They will perform the test before they start the study and will continue to perform it every 6 weeks during the study period while receiving either PTC124 or a placebo. If, over the study period, PTC124 safely allows participants to walk a longer distance than the participants who receive the placebo, this may provide the necessary evidence required by the regulatory authorities to show that PTC124 improves functioning.

To ensure that that the Phase 2b study has a good chance of success, it is important that participants are old enough to perform the 6-minute walk test repeatedly and consistently. It is known from past experience that children under the age of 5 years have difficulty performing the 6-minute walk test reliably. The scientific literature bears this out. Most recently, a study reported in the April 2007 *Journal of Pediatrics* (Ralf Geiger MD et al, "Six Minute Walk Test in Children and Adolescents") found that only 39% of children in the 3- to 5 year-old age group were able to understand and complete the test, compared to 93% of older children. For this reason, children who are younger than 5 years of age cannot be included in the Phase 2b study.

5. Q: Why are patients with Becker muscular dystrophy (BMD) being included in the Phase 2b trial now when they weren't in the earlier clinical trials of PTC124?

A: DMD and BMD, rather than being distinct diseases, represent a continuum of the same disease. A mutation in the dystrophin gene is the cause for both DMD and BMD; however, the types of mutation in patients with BMD appear to cause less rapid loss of muscle function. Because changes in muscle function vary among patients, it is not always clear whether a particular patient should be defined as having DMD or BMD. Thus, as long as an ambulatory patient has the diagnosis of DMD or BMD due to a nonsense mutation and is having trouble walking due to the disease, there is no known reason to exclude him.

In order to be able to show improved functioning in trial participants, enrollment is limited to those patients with BMD who had medically documented signs of their disease, such as elevated creatine kinase, muscle weakness, waddling gait, and Gowers' maneuver by age 9, and are having problems with walking. These criteria indicate that they have problems due to their BMD/DMD that make it appropriate for them to consider an investigational drug like PTC124. The decision as to whether a patient is appropriate for the study is ultimately made by the principal investigator at the study site, who is best able to weigh the potential risks and benefits for each potential participant.

6. What does participation in the Phase 2b DMD/BMD trial involve?

Before being considered for enrollment in the study and before undergoing testing or receiving study medication, a patient (and a parent or guardian, if the patient is minor) must be informed about the study by the medical researchers. They must sign a document called an informed consent form indicating a willingness to participate. This

document explains the trial in great detail to allow patients to assess the risks and benefits of participation. A copy of the informed consent form is provided to each patient.

Thereafter, the patient undergoes screening evaluations to determine whether he is qualified to participate in the study. These screening procedures will usually be done at 2 separate clinic visits during the 6-week period before treatment would be started. The purpose of these screening evaluations is to determine whether a person's participation in a clinical trial meets the study entrance requirements and can contribute data that will help achieve the study goals.

In order to determine if PTC124 improves symptoms of DMD/BMD and to understand what dose level can be given safely, it is necessary to compare participants receiving different dose levels of PTC124 with participants who are not receiving PTC124. The amount of drug used is determined by body weight in kilograms (1 kilogram equals 2.2 pounds).

The participants will be divided into 3 groups of about 55 patients each:

- Group 1: High-dose PTC124 (20 milligrams per kilogram [mg/kg] in the morning, 20 mg/kg at midday, and 40 mg/kg in the evening)
- Group 2: Low-dose PTC124 (10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening)
- Group 3: Placebo (inactive drug powder that looks and tastes the same as PTC124), given, in the morning, at midday, and in the evening)

Each participant will be randomly assigned to 1 of the 3 groups, meaning that he will be put into a group by chance. This is done by a special computer program. Because there is an equal chance of going into any of the groups, this means that each participant has a 2 out of 3 chance of receiving PTC124 (either in the high-dose or low-dose groups) and a 1 out of 3 chance of receiving placebo. The patient, the patient's family, the study investigators, and PTC Therapeutics personnel cannot choose the group and cannot know which treatment each participant is receiving until after the study is over.

The drug or placebo is supplied in an aluminum foil packet and has a mild vanilla-flavor. It is mixed in water or milk and taken 3 times per day for 48 weeks.

During the 48 weeks of treatment, a 2-day clinic visit will be required every 6 weeks; at these clinic visits, participants will perform the 6-minute walk test and will have other evaluations. They will take home activity monitors to see how much they are walking at home and during daily activities. During the first 24 weeks of treatment, participants will visit the research site or a local laboratory every 3 weeks for collection of additional blood and urine for safety tests.

Upon successful completion of this study, participants will have the opportunity to enter into an extension study in which every participant will receive PTC124. 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 study drug to document the general health of the participant. In addition, each patient or parent will be asked to complete a short survey on general health at 6- to 12-month intervals over a 5-year period. This survey may be completed at the clinic during a routine visit or by telephone.

7. Q: Will use of corticosteroids such as prednisone or deflazacort affect who can participate in the Phase 2b DMD/BMD trial?

A: No. Participation in the trial is open to patients whether they are taking corticosteroids or not. However, it is important that participants not make a change by starting or stopping corticosteroids or adjusting the dose during the study. Thus, participants in the study who are not using corticosteroids when they start the study should avoid starting corticosteroids for the 48 weeks of the trial period. Participants in the trial who are taking corticosteroids may continue to take them. However, patients who are taking corticosteroids must have initiated corticosteroid therapy at least 6 months before enrolling in the trial and must not have changed their dose for at least 3 months before enrolling in the trial. Dose adjustments necessitated by increased body weight are allowed.

8. Q: Where is the Phase 2b DMD/BMD trial being conducted and how long will the trial be accepting patients?

A: Study sites are planned in Australia, Belgium, Canada, England, France, Germany, Israel, Italy, Spain, Sweden, and the United States. As soon as each site is open to enroll patients, contact details for the site are listed on www.clinicaltrials.gov and www.ptcbio.com/PTC124_clinical_trial_locations. The study will continue enrolling new patients until the necessary number of participants has been reached. It is estimated that enrollment will end in early 2009. The sooner patients enroll in the study, the faster the study can be completed, and the sooner the results can be known.

9. Q: How can a patient with DMD/BMD enroll in the Phase 2b study?

A: As soon as sites are open, contact details will be posted and participants or their families can contact a site directly to inquire about study participation. Personnel at the site will explain the study procedures and the potential benefits and risks associated with participation. Potential participants will be given an informed consent form further explaining the trial; those choosing to sign the form will be screened and considered for enrollment.

10. Q: Is there any cost to participate in the trial?

A: 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.

11. Q: Why is this a Phase 2b trial and not a Phase 3 trial? Will a Phase 3 trial still be necessary?

This is considered a Phase 2b trial rather than a Phase 3 trial because one of its objectives is to determine the optimal dose of PTC124 by testing 2 different dose levels. Typically, an optimal dose level is determined in a Phase 2 trial before a Phase 3 study is done. However, if the Phase 2b trial results are sufficiently positive, the data from this trial could potentially be submitted to the FDA, to the EMEA, and to other regulatory authorities for approval without the need to perform a Phase 3 trial.

12. Q: Is there any way to get PTC124 outside of a clinical trial?

A. PTC124 is an investigational drug that has not yet been approved for sale by regulatory authorities in any country and thus cannot be legally purchased for use by a patient. The only form of PTC124 that meets regulatory requirements for safety and purity and is appropriate for use in humans is manufactured by PTC Therapeutics. Because it is an investigational drug, PTC124 is being provided by PTC Therapeutics only for use in clinical trials.