Progress Update for Drug Discovery Program to Identify Novel Treatments for Duchenne Muscular Dystrophy

PTC Therapeutics and Parent Project Muscular Dystrophy (PPMD) are collaborating to discover new drugs to treat Duchenne muscular dystrophy (DMD). The project is focusing on 5 targets, or proteins related to DMD. It is expected that increasing or decreasing the amount of these proteins in boys with DMD will help to treat the disease. Our progress in each of the 5 areas is described below.

**Target 1:** We previously tested a lead compound in a mouse model of DMD (mdx mice) and observed positive results. More recently, we developed a formulation of the compound that can be administered for longer periods, allowing the body to maintain over time a concentration of the compound that is high enough to achieve the desired effect. A pilot experiment with the new formulation was successful, and this lead compound is now ready to be evaluated for longer periods of time in mdx mice. We also have identified several other promising compounds and are currently optimizing them – adding something here or removing something there, over and over again, and testing all of these variations, or analogs, to determine which are the most promising. To perform this testing, it is necessary to have a fast and reliable test, or assay. We are close to finalizing the development of a 3-step assay that is far simpler than the standard assay and will allow us to rapidly screen a large number of compounds. This new assay, when finalized, will help to expedite the lead optimization process.

**Target 2:** When a drug is administered into the body, the efficacy of the drug may depend on how much of the drug goes to the part of the body where it is needed. We previously tested a compound of interest in mice and determined that sufficient quantities were distributed to relevant muscle tissues. More recently, we tested this compound and several other promising compounds in a mouse cell line to determine whether, as hoped, they decreased the amount of the target protein. Reductions of 50 to 75% were achieved, paving the way for proof-of-concept studies in a mouse model of DMD.

**Target 3:** We have synthesized and tested over 500 analogs and are currently studying whether they hit the target only (more selective) or the target and other proteins (less selective); how they are metabolized by the body; how potent they are; and how narrow or wide is the margin between the dose that is high enough to achieve the desired affect and the dose that is too high and causes toxicity. We have recently synthesized a sufficient quantity of 1 compound to initiate a pharmacokinetic study in dogs. If the results are positive, the next step will be to conduct an efficacy study in dogs.

**Target 4:** We have conducted pharmacokinetic studies of several promising compounds in mice; these studies showed that 24 hours after administration, the compounds remained in the body at concentrations that were effective in prior cell line experiments. Based on these data, we have synthesized sufficient quantities of the compounds in order to perform proof-of-concept studies in mdx mice. These experiments are currently ongoing.

**Target 5:** Our initial screening effort identified over 2,000 hits. The next step is to “cherry-pick” the most promising of these and re-screen them to confirm the results of the initial screen. This is scheduled to occur in 3Q2008. We also are preparing and evaluating materials to be used in future studies.

In summary, we are enthusiastic about the progress we have made to date for each of the targets of interest and look forward to the next quarter.

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