Ataluren Update July 2012

Summary of trial results

The pivotal Phase 2b trial of ataluren, an investigational new drug being studied in nonsense mutation Duchenne/Becker muscular dystrophy (DBMD), was completed in late 2009. It had enrolled 174 patients at 37 trial sites in 11 countries on four continents. As PTC and statistics experts have analyzed the complex data from this trial using various statistical methods, the company has come to understand that the results are very promising.

Efficacy

- The trial had low-dose ataluren and high-dose ataluren arms as well as a placebo arm. The main criterion, or endpoint, used to determine differences in performance among the three arms was the Six Minute Walk Test, which measured, every six weeks, the distance that participants could walk in 6 minutes (6MWD).
- Participants receiving low-dose ataluren (10, 10, 20 mg/kg) showed a clinically meaningful difference (approximately 30 meters) in the change in their 6MWD results when compared to the placebo arm.
- The FDA requires that trial sponsors specify in advance which statistical models will be used to analyze data at the end of a study. The data was first analyzed using the pre-specified statistical method. The unexpected complexity of the ataluren data could not be fully addressed using this method, so it was necessary to use a different (ie, post hoc) statistical model to fully understand the results.
  - A post hoc statistical analysis, using a model suggested by independent statistics experts, showed an average difference between low-dose ataluren and placebo of 31.3 meters (103 feet) in the 6MWD. The p-value for this result is 0.0561. A p-value is a test of statistical significance that measures how likely it is that a result is due to an actual effect rather than to chance. In this case, the post hoc corrected p value of 0.0561 indicates that there is only about a 5% possibility that the results could have been obtained if ataluren was no different than placebo.
  - A second measure used to compare the effects of ataluren at the two different doses and against placebo was the time it took for the 6MWD to worsen by 10% and remain so. This was defined as "time to persistent 10% worsening." This analysis indicated that patients receiving low-dose ataluren experienced slower disease progression than patients receiving placebo. By the end of the trial, 26% of the low-dose patients were persistently 10% worse in 6MWD than when they started, compared to 48% in the high-dose arm and 44% in the placebo arm (post hoc p=0.0652 for low-dose ataluren vs placebo).
- The 6MWD results from the high-dose (20, 20, 40 mg/kg) arm were similar to the placebo arm. At the completion of the preliminary data analysis, all patients in three ongoing DBMD clinical trials (Phase 2a and 2b extension studies and a non-ambulatory study) were receiving the high dose. Although an independent data monitoring committee agreed that ataluren was well tolerated by patients, the committee recommended that the trials be suspended because all patients in ongoing trials were on the high dose.

Safety

- Safety results showed that ataluren was generally well tolerated:
  - Adverse events were similar across all three arms of the study: high-dose, low-dose and placebo.
  - No patients discontinued treatment due to an adverse event.
  - Serious adverse events were infrequent and none was considered to be related to ataluren.

Current status

Extension Studies

- In the US, PTC is providing access to ataluren to 106 previous trial participants through an open-label study in which all patients receive ataluren (10, 10, 20 mg/kg). Safety data is being collected. Enrollment in this trial is complete and patients have been receiving ataluren for at least six months.
- In Canada and nine other countries that had Phase 2b trial sites, PTC has initiated an open-label study, collecting safety and efficacy data. Several patients have already been enrolled and are now receiving drug. Many sites are in various stages of obtaining national and local regulatory permission and completing paperwork to enroll patients over the next several months.

Regulatory Path

- PTC remains committed to the development and commercialization of ataluren and is engaged in discussions with regulatory authorities in the US and Europe regarding the path forward for ataluren in nonsense mutation Duchenne/Becker muscular dystrophy.

- The FDA feedback is that the efficacy data from the single Phase 2b trial is not adequate to support approval at this time.
  - When the FDA is presented with data from a single pivotal trial, even for a rare disease, the data has to meet a particularly high standard. Discussions with the FDA regarding ataluren and the path forward are still ongoing.
  - The FDA considers a p-value of 0.05 to be the standard criterion for statistical significance. This means that there is no more than a 5% chance that the trial results were due to chance and not to an actual drug effect. The corrected post-hoc analysis showed a p-value of 0.0561 for the comparison of low-dose ataluren vs. placebo in the 6MWD.
  - The ataluren Phase 2b study was the first registration-directed trial ever conducted in DBMD and it was not known what the clinical endpoints, some of which had never been used before, would show when measuring the impact of a disease-modifying therapy.
  - Several other factors contributed to the difficulty of obtaining more robust evidence of efficacy in this trial, including the variability in the natural history of DBMD, the requirement to pre-specify the statistical analysis in the absence of a previous trial that could act as a model, and the limitations of doing trials in rare diseases.
  - The most likely outcome of our FDA discussions is that a pre-approval confirmatory study will be necessary.

- The company is simultaneously in discussions with the European Medicines Agency (EMA) concerning the path forward in Europe. It is possible that we will be able to file in the European Union under the mechanism of conditional approval, in which approval is granted with the requirement to conduct a confirmatory study.
  - PTC is engaged in the formal scientific advice process of presenting data from the trial to selected regulatory officials for their input. The precise timing of the filing, however, will depend on the outcome of our upcoming meetings. We are encouraged by discussions with the EMA thus far.

Confirmatory study

- Whether in the context of conditional approval in Europe, or to meet additional requirements in the US, PTC is currently planning to conduct an additional confirmatory study of low dose ataluren (10, 10, 20 mg/kg) vs. placebo.

- This study design will be based on the Phase 2b trial results and the goal is to confirm the previous findings in the low-dose patient group.
- PTC is in discussions with clinical investigators and regulatory agencies about the specific design and endpoints for this trial and will update the community when a protocol is finalized.
- It is important to realize that a confirmatory study is often more restrictive in its inclusion/exclusion criteria than the original trial, as it is intended to confirm specific results. The goal of the clinical trial is to secure approval of ataluren so all patients who might benefit from ataluren may have access.