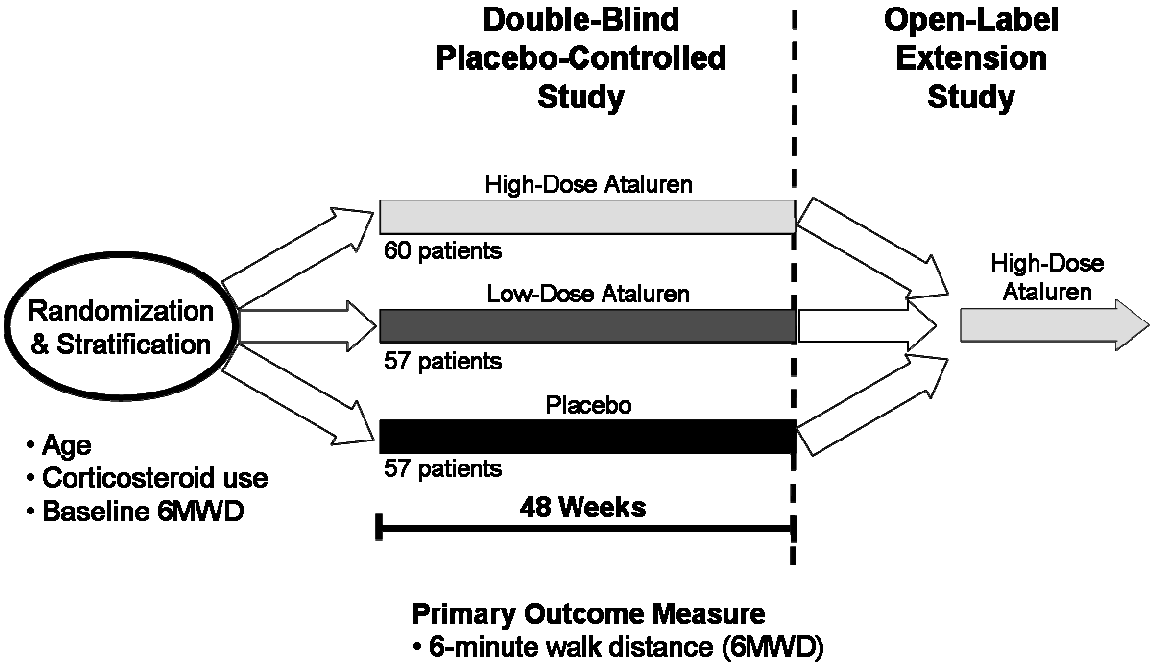
Summary of Ataluren Phase 2b Clinical Trial Results
Presented at the American Academy of Neurology Meeting on April 16, 2010

An investigational (experimental) new drug discovered by PTC Therapeutics, ataluren is being developed for commercialization by PTC Therapeutics and Genzyme Corporation in an exclusive global collaboration. Ataluren is designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation. A nonsense mutation is an alteration in the genetic code that prematurely stops the production of a protein essential to the proper functioning of the body. The resulting disease is determined by which protein cannot be fully formed and is no longer functional, such as the dystrophin protein in nonsense mutation Duchenne and Becker muscular dystrophy (nmDBMD).

Phase 2b Clinical Trial Design

The Phase 2b trial of ataluren was the largest and longest study of an investigational new drug ever conducted in patients with DBMD. It enrolled 174 boys and young men ages 5 to 20 years at 37 trial sites in 11 countries. Through gene sequencing analysis, all of the patients in the trial were known to have DBMD due to a nonsense mutation. Participants were randomly assigned (randomized) to receive a placebo, low-dose ataluren, or high-dose ataluren for 48 weeks. In addition, participants were evenly distributed (stratified) across these three treatment arms by age, corticosteroid use, and baseline 6-minute walk distance (6MWD).



The primary goal of the Phase 2b trial was to evaluate whether ataluren showed clinical benefit. A drug is judged to have clinical benefit when it improves how patients feel, function, or survive. Because this was the first registration-directed clinical trial conducted in patients with DBMD, there was no precedent for a primary endpoint known to be acceptable to regulatory authorities. The primary endpoint chosen to determine clinical benefit was a change in walking ability as shown by a change in the distance walked in 6 minutes (performed as part of a 6-minute walk test [6MWT]) when evaluated periodically over 48 weeks. Regulatory agencies are familiar with the 6MWT and it has supported the approval of multiple drugs for other disorders as a primary endpoint in clinical trials. Major secondary endpoints included changes in muscle function, muscle strength, and dystrophin expression.

Overall, the compliance with study procedures was excellent. Patients took about 97 percent of their assigned doses as planned. In addition, almost all patients who were taking a corticosteroid (such as prednisone or deflazacort) when they entered the study made no changes in their corticosteroid regimens during the trial.

Safety Results

The safety results from the study showed that ataluren was well tolerated at both dose levels. Adverse events were similar among patients receiving placebo and patients receiving low-dose or high-dose ataluren. No patients discontinued treatment due to an adverse event. Serious adverse events were infrequent and none were considered to be related to ataluren. The most common adverse events (including vomiting, headache, and diarrhea) were consistent with symptoms not uncommon in young patients.

Planned Analysis of Efficacy Results

Before a clinical trial is conducted, the sponsor has to specify, in agreement with the regulatory authorities, how data will be collected and analyzed. For the Phase 2b trial, the following analyses were agreed to:

1. The analysis of 6MWT results was expected to show an average increase of 30 meters (about 33 yards) from baseline to Week 48 in at least one of the ataluren treatment groups compared to the placebo group.

2. A commonly used method of statistical analysis called RANCOVA would be the primary method used to determine the statistical confidence level of the 6MWT results. A high statistical confidence level, also called statistical significance, indicates that a result is unlikely to have occurred by chance. In this study, a target statistical confidence level of 95% was pre-specified. In general, the statistical analysis of clinical trial results is very important to regulatory authorities when considering whether to approve an investigational new drug.

3. Another type of analysis would be used to determine the amount of time it took for patients in the study to experience a decrease of 10% in 6MWD. This is known as time to persistent 10% worsening.

Efficacy Results

Based on the pre-specified criteria for analyzing the trial results, the efficacy results are summarized below:

1. At 48 weeks, the difference in average change in 6MWD between the low-dose ataluren group and the placebo group was 29 meters (about 32 yards), one meter below the predicted outcome (Figure 1). The average change in 6MWD in the low-dose ataluren group was a decrease of 13 meters (14 yards). The high-dose ataluren and placebo groups had the same average change in 6MWD, a drop of 42 meters (46 yards). In addition, the improvement in 6MWD among patients receiving low-dose ataluren compared to patients receiving placebo was generally consistent regardless of patients' age, use of corticosteroids, or walking ability at the beginning of the study.

2. With the RANCOVA method, the difference between the low-dose ataluren group and the placebo group demonstrated a 29-meter difference with an 85% confidence level, below the 95% confidence level pre-specified for this study. A different statistical analysis method called ANOVA showed that the difference in the average 6MWD between patients receiving low-dose ataluren and patients receiving placebo was within the 95% confidence level. The use of the ANOVA method, however, was not pre-specified in the statistical analysis plan.

3. The pre-specified analysis of the time to persistent 10% worsening in 6MWD indicated that patients receiving low-dose ataluren experienced slower disease progression (Figure 2). These results were within the 95% confidence level.

In addition, the efficacy results obtained using the 6MWT demonstrated greater variability than anticipated. This might have been due to differences in the rates of disease progression in certain boys, differences in performance from patient to patient, or differences in an individual's performance over time.

Figure 1: Difference between the treatment groups in the average 6MWD through 48 weeks of treatment

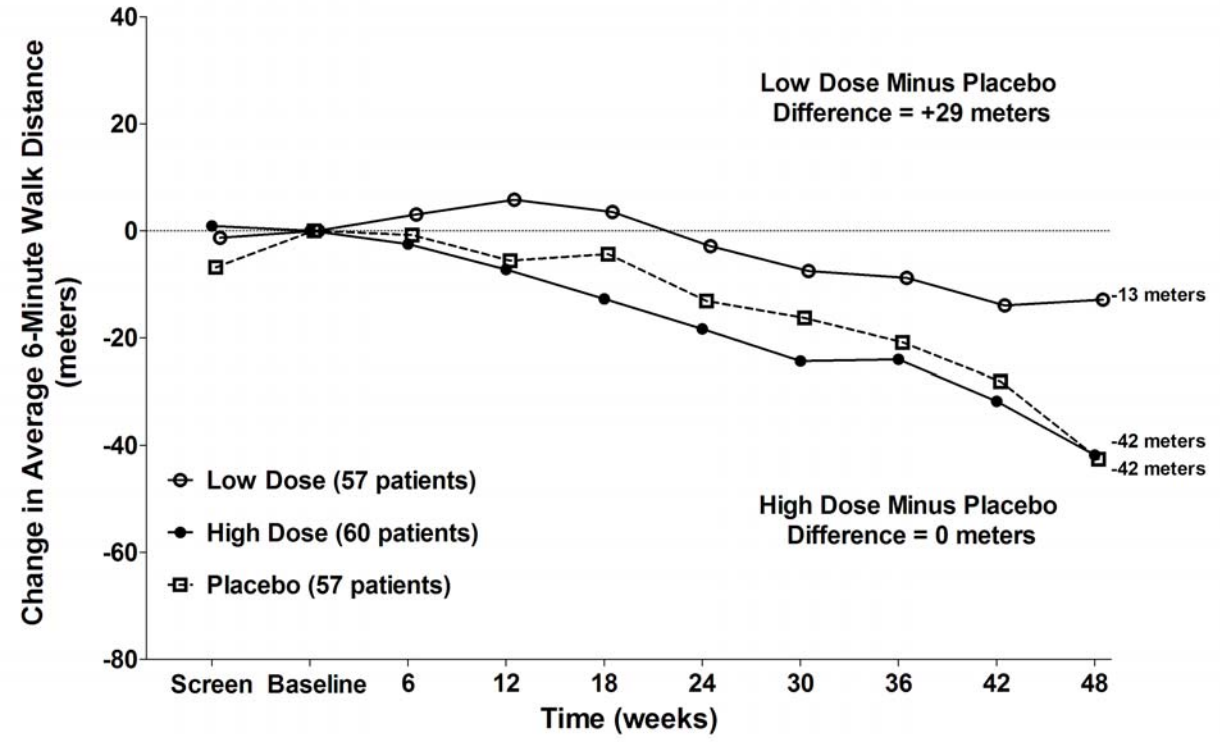
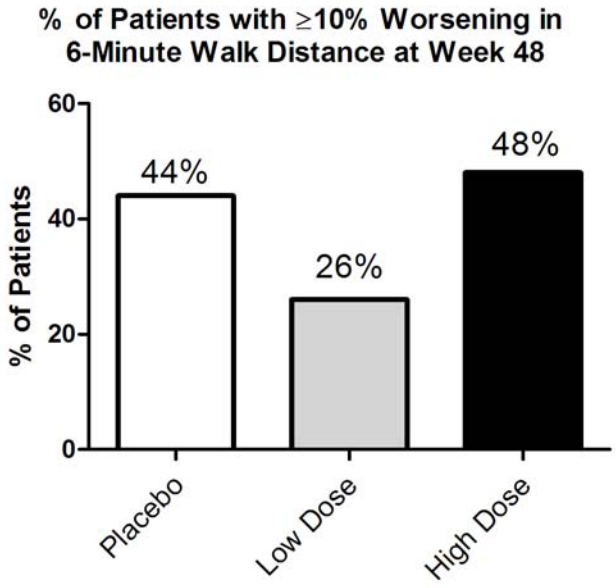


Figure 2: Percent of patients with 10% worsening in 6MWD at week 48



Conclusions

The safety and efficacy results from the trial lead to the following conclusions:

- Overall, the study was well conducted
- Ataluren was well tolerated across both treatment arms compared to placebo
- Variability of the change in 6MWD was greater than expected
- The high-dose ataluren group did not show a treatment effect (a difference in outcome from the placebo group)
- The low-dose ataluren group showed a mean improvement in 6MWD compared to the placebo group

Importantly, at the completion of the preliminary data analysis, all patients in ongoing DBMD clinical trials were receiving the high dose of ataluren. Although an independent data monitoring committee (DMC) agreed that ataluren was well tolerated by patients, the DMC recommended that the trials be suspended because of the lack of a treatment effect at the high dose of ataluren and because all patients in ongoing trials were receiving this high dose.

Next Steps

Further data analyses are needed to understand the potential efficacy of low-dose ataluren as a treatment for patients with nmDBMD and to determine the appropriate clinical and regulatory path forward for the drug.

Evaluations of secondary endpoints are ongoing. Additional analyses of data from previous studies with ataluren and other drugs with a similar mechanism of action (for example, aminoglycoside antibiotics that promote nonsense mutation readthrough) are also being conducted.

These analyses will help us better understand why patients receiving low-dose ataluren experienced better outcomes than patients receiving high-dose ataluren. This observation suggests that ataluren may have an inverted U- or bell-shaped dose-response curve. This type of inverted U-shaped dose-response phenomenon is not unique to ataluren and has been observed with other drugs for other diseases. As these analyses are completed, PTC Therapeutics and Genzyme expect to present new results at additional scientific meetings in 2010.

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