Ataluren Phase 3 trial results in nonsense mutation cystic fibrosis

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PTC Therapeutics, Inc. today announced that the results of a Phase 3 study of ataluren in patients with nonsense mutation cystic fibrosis (nmCF) were published in *Lancet Respiratory Medicine*. The results demonstrated positive trends in both the primary endpoint, lung function as measured by relative change in % predicted FEV1 (forced expiratory volume in one second) and in the secondary outcome measure, rate of pulmonary exacerbations. The collective data from this trial, including retrospective and subgroup analyses support the conclusion that ataluren was active and showed clinically meaningful improvements over placebo in these trials.

"The overall data from this trial are promising. Patients on ataluren experienced fewer pulmonary exacerbations and showed a stabilization in their FEV1 results, particularly in the subgroup of patients that did not use chronic inhaled aminoglycosides. Such stabilization of disease is an important clinical endpoint, particularly for this patient population that has one of the most severe forms of CF. CF patients with nonsense mutations do not produce any functional CFTR protein and therefore generally have a more severe form of cystic fibrosis. Current treatments for nonsense mutation cystic fibrosis focus on alleviating symptoms and reducing infections, whereas ataluren targets the underlying cause of disease," stated Michael Konstan, M.D., lead study investigator and Chairman of Pediatrics at from University Hospitals Rainbow Babies and & Children's Hospital in Cleveland, Ohio.

The Phase 3 double-blind, placebo-controlled study, which was

conducted across 11 countries, compared ataluren (n=116) to placebo (n=116) in nmCF patients. The primary endpoint, the relative change from baseline in %-predicted FEV1 at 48 weeks, showed a positive trend favoring ataluren versus placebo, and a larger effect in patients not receiving chronic inhaled tobramycin. In the intent-to-treat population, there was a 3% difference in the relative change from baseline in %-predicted FEV1 between the ataluren and placebo groups at Week 48 (-2.5% change on ataluren vs. -5.5% change on placebo; p=0.12) which was not statistically significant. An analysis of the relative change from baseline in %-predicted FEV1 across all post-baseline study visits demonstrated an average difference between ataluren and placebo of 2.5% (-1.8% average change on ataluren vs. -4.3% average change on placebo; p= 0.048). There were 23% fewer pulmonary exacerbations in the ataluren group compared to placebo (p=0.0992). Further results from a post hoc analysis of the subgroup of patients not receiving chronic inhaled tobramycin showed a 5.7% difference in relative change from baseline in % predicted FEV1 favoring ataluren, with a mean change from baseline of -0.7% in the ataluren arm, and – 6.4% in the placebo arm (nominal p=0.0082). In addition, there were 40% fewer exacerbations in ataluren-treated patients in this subgroup. The outcomes observed in multiple endpoints between the subgroup of patients who were not prescribed chronic inhaled tobramycin and the subgroup of patients who were prescribed chronic inhaled tobramycin as well as post-hoc in vitro testing showing the interference of aminoglycoside antibiotics with ataluren activity support the hypothesis that inhaled tobramycin may interfere with ataluren's mechanism of action.

Safety results indicate that ataluren was generally well tolerated. The overall incidence of adverse events through Week 48 was similar in the ataluren and placebo groups, except for the occurrence of creatinine elevations that occurred more frequently in the ataluren group in connection with concomitant treatment with systemic aminoglycosides. Most treatment emergent adverse events were of mild (Grade 1) or

moderate (Grade 2) severity, and no life-threatening adverse events were reported. Most serious adverse events reported in this study were CF pulmonary exacerbations and were considered unrelated to ataluren treatment. Eight patients in the ataluren arm and three patients in the placebo arm discontinued treatment due to an adverse event.

"We are very encouraged by the data from this trial. Given spirometry and pulmonary exacerbation results in the subgroup of patients not receiving chronic inhaled tobramycin, and a favorable safety profile, this study supports further clinical testing of ataluren as a potential first-in-class treatment for nmCF patients not receiving chronic inhaled tobramycin," stated Stuart W. Peltz, Ph.D., Chief Executive Officer of PTC Therapeutics, Inc. "We look forward to initiating a confirmatory ataluren trial in nmCF patients later this year."

Provided by University Hospitals Case Medical Center