News Release

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ATS Press Room: 504-670-6926 (May 15 to 20)

Poster session time: 1:30-4:00 p.m. May 16
Location: CC-Room 388-390 (Third Level), Morial Convention Center

MP-376 Safe and Effective for Treatment of *P. aeruginosa* in CF Patients

ATS 2010, NEW ORLEANS— A new possible treatment to treat *P. aeruginosa* in cystic fibrosis (CF) patients appears to be promising, according to research to be presented at the ATS 2010 International Conference in New Orleans.

Approximately 80 percent of CF patients develop chronic *P. aeruginosa* lung infection, and antibiotic resistance is an increasing problem. "New classes of inhaled antimicrobials are necessary to treat CF patients with chronic *P. aeruginosa* lung infection due to concerns for increased antimicrobial resistance, decreased efficacy and poor compliance/tolerability with currently available agents," said lead author of the research, Douglas Conrad, M.D., an associate professor of medicine at the University of California, San Diego.

To test the efficacy and safety on the new antibiotic called MP-376, a levofloxacin inhalation solution, the researchers recruited 151 CF patients and randomized them to receive MP-376 at three different dosing levels [120mg once a day (QD); 240 mg once a day, or 240mg twice a day (BID)] or placebo. Inhaled antimicrobials are known to be effective in lowering organism load in the airways and improving lung function in CF patients.

On average, the patients were 29 years old, had received almost five courses of inhaled antibiotics active against *P. aeruginosa* in the past year, were on multiple treatments to control their CF lung disease, and had just slightly more than 50 percent of predicted lung function for healthy individuals.

After 28 days of treatment, patients receiving MP-376 had reduced *P. aeruginosa* density in their sputum compared to those who had received placebo, and showed no evidence of antimicrobial resistance. The greatest significant treatment effect observed was in the patients who received the highest dose of MP-376 of 240mg twice a day. Eight patients discontinued the study, six due to adverse events. Of these six patients, two were in the placebo group, one in the 120mg QD, one in the 240mg QD and two in the 240mg BID group.

Lung function also improved in all the MP-376 groups with the greatest improvement being seen in those who received the 240mg BID dose, with an average improvement in $FEV_{1\% \text{ predicted}}$ of 10.9 percent over placebo. A similar effect was also seen in other measures of lung function.

Furthermore, treatment with MP-376 reduced the need for treatment with other anti-pseudomonal antimicrobials, with a 79 percent reduction over placebo in the MP-376 240mg BID group.

“MP-376 was well tolerated with no evidence of an increasing adverse event profile with increasing dose and adherence to MP-376 was very good with over 80 percent of patients in the study taking more than 90 percent of their drug,” said Dr. Conrad.

While the reduction in *P. aeruginosa* density was expected, the degree of lung function improvement and reduction in the need for other antipseudomonal antimicrobials in this heavily treated patient population was unanticipated.

“The vast majority of patients were receiving dornase alpha, azithromycin and/or hypertonic saline, all of which on their own have been shown to improve lung function. Patients in the study had also received a mean of 4.8 courses of inhaled antimicrobials over the preceding 12 months, so a treatment effect of over 10 percent in percent predicted FEV1 in the MP-376 240mg BID group was unexpected,” said Dr. Conrad.

Phase 3 trials are scheduled to begin later this year. “Positive findings in Phase 3, and subsequent regulatory approval, would provide CF clinicians with another important class of inhaled antimicrobials to treat CF lung disease,” said Dr. Conrad. “Prevention of exacerbations and preservation of lung function are very important to patients with chronic *P. aeruginosa* lung infection and based on this study, we would expect similar results with MP-376 in Phase 3 studies. MP-376 would provide patients with a well tolerated inhaled antimicrobial that can be taken twice per day with a nebulization time of only 4-6 minutes, thus significantly lowering the treatment burden over currently available agents.”

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“Phase 2b Study of Inhaled MP-376(Aeroquin, Levofloxacin Inhalation Solution) in Stable Cystic Fibrosis (CF) Patients with Chronic Pseudomonas Aeruginosa (PA) Lung Infection” (Session A102, Sunday, May 16, 1:30- 4:00 p.m., CC-Room 388-390 (Third Level), Morial Convention Center; Abstract 420)

**Please note that numbers in this release may differ slightly from those in the abstract. Many of these investigations are ongoing; the release represents the most up-to-date data available at press time.*

Phase 2b Study of Inhaled MP-376 (Aeroquin, Levofloxacin Inhalation Solution) in Stable Cystic Fibrosis (CF) Patients with Chronic *Pseudomonas aeruginosa* (PA) Lung Infection

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Introduction: New inhaled antimicrobial agents for CF patients are needed due to increased antibiotic resistance, decreased efficacy and poor compliance/tolerability. MP-376 is a novel aerosol formulation of levofloxacin delivered via a customized investigational PARI eFlow nebulizer. This study was designed to assess the efficacy and safety of MP-376 over 28 days of dosing in a heavily treated CF population.

Methods: A randomized, double-blind, placebo controlled trial of 3 dose groups of MP-376 (120mg QD, 240mg QD, 240mg BID) vs. placebo administered for 28 days. Inclusion criteria were a diagnosis of CF, age $\geq$ 16 years, chronic PA airways infection, FEV1 between 25-85% predicted, and at least 3 courses of inhaled antibiotics over the past 12 months. The primary endpoint was change in sputum PA density over the 28 days of treatment. Other efficacy endpoints included change in lung function, reduction in the need for systemic or other inhaled anti-PA antimicrobials, and patient reported outcomes (CFQ-R).

Results: 151 patients were enrolled. Eight patients (5%) discontinued the study. Mean baseline characteristics were age 29 years, FEV1 52% of predicted, and receipt of 4.8 courses of inhaled antibiotics over last 12 months. Concomitant respiratory medications included dornase-alpha (78%), azithromycin (74%), and hypertonic saline (46%). A reduction in sputum PA density at Day 28 in the combined 240mg MP-376 dose groups vs. placebo was observed ($p=0.0002$), with all MP-376 groups being statistically better than placebo ($p < 0.01$ for all groups), with no emergence of resistance. A greater proportion of patients had improvement in FEV1 (% predicted) with any dose of MP-376 compared to placebo, with a difference of 10.9% in FEV1 between the 240mg BID group and placebo ($p=0.0008$). A reduction in the need for other inhaled and/or systemic anti-PA antimicrobials was observed in all MP-376 groups vs. placebo (risk reduction of 61-79% for all groups; MP-376 240mg BID vs. placebo HR=0.21; $p=0.0007$). A difference of 6.4 points in the pulmonary domain of the CFQ-R was observed between MP-376 240mg BID and placebo ($p=0.09$). The percent of patients with AEs was similar across all groups, with no evidence of increasing incidence or severity of AEs with increasing MP-376 dose.

Conclusion: Nebulized MP-376 (Aeroquin) was well tolerated and demonstrated statistically and clinically significant efficacy compared to placebo across multiple