INTRODUCTION

- Bronchiectasis is one of the most neglected diseases in respiratory medicine. In NCBE patients, infections with PA are associated with an increase in hospital admissions and pulmonary exacerbations (PEs), and a 3-fold increase in mortality compared to NCFBE patients without PA.
- Inhaled antibiotics and recombinant human DNase have been successfully developed for the prevention of PEs in cystic fibrosis (CF) patients colonized with PA. It was found that early attempts to develop such treatments outside CF have so far failed due to lack of efficacy and problematic safety and tolerability.
- Consequently, there is no approved treatment available to prevent PEs in this condition, resulting in an urgent medical need to develop a safe and effective therapy for NCBE patients colonized with PA.

OBJECTIVES

Pulmaquin (ARD-3150), a unique once-a-day inhaled dual-release formulation composed of a mixture of liposome encapsulated and unencapsulated ciprofloxacin, is being evaluated in 2 identical phase III trials (ORBIT-3 and ORBIT-4) in adult patients with CF-1-screened NCBE who have chronic lung infections with PA. The trials compare the efficacy and safety of ORBIT-3, using the same time and dosage regimen as in the current Phase III program, showed a significant PA bacterial load reduction in sputum of 27,000 fold (4.4 log) with ARD-3150 and a significant prolongation in the median time to first pulmonary exacerbation compared to placebo (from 58 to 124 days). The summary of AEs indicated similarities of AEs and SAEs in the two treatment groups but a favorable pulmonary A/E profile in the ARD-3150 group compared to placebo.

METHODS

Mortality Major Eligibility Criteria
- Patients must have a medical history of PA infection, had at least 2 PEs in the 12 months prior to enrollment, and a documented positive sputum sample with at least one PA isolate nonencapsulated to ciprofloxacin.
- Patients with active non-TB mycobacterial infections are included as long as they are not currently being treated with an antibiotic.
- Patients with chronic macrodose treatment at baseline are included.

Study Design and Assessments
- Each trial has a 48-week blind period of 6 cycles of 28 days on and 28 days off treatment comparing ARD-3150 to placebo, followed by a 28-day open label extension with ARD-3150.
- The primary endpoint is time to first PE during the double blind phase.
- Key secondary endpoints are the number of PEs, severe PEs and quality of life (QOL-L, respiratory domain) during the double blind phase.
- Other endpoints include microbiology assessments (PA density, ciprofloxacin MIC for PA, isolation and quantification of PA), spirometry (FEV1 and FVC), DLCO and adverse events as safety indicators.
- The Respiratory Domain of the QOL-B is an important secondary endpoint in ORBIT-3 and -4, assessed prior to the first dose of study drug and then every 28 days at each on-site study visit.

RESULTS

- The summary of AEs indicated similarities of AEs and SAEs in the two treatment groups but a favorable pulmonary A/E profile in the ARD-3150 group compared to placebo.
- The two well-controlled clinical trials ORBIT-3 and -4 will provide a large database of well-defined NCBE patients with chronic PA colonization to investigate the effect of ARD-3150 on the prevention of PEs using a rigorous definition of exacerbations.
- Assessments of microbiology, quality of life, PK analysis and other endpoints will provide a comprehensive analysis of the benefit of ARD-3150.

SUMMARY AND CONCLUSIONS

- The open label extension with 20 day ARD-3150 treatment will provide additional information on the safety and effect of ARD-3150 for the management of PA infected patients with chronic CF.

REFERENCES