ORBIT-3 and ORBIT-4: Design of a Phase 3 Program to Investigate Safety and Efficacy of Pulmaquin® in Non-Cystic Fibrosis Bronchiectasis (NCFBE) Patients Chronically Colonized with *Pseudomonas Aeruginosa* (PA)

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INTRODUCTION

- Bronchiectasis is one of the most neglected diseases in respiratory medicine.[1] In NCFBE patients, infections with PA are associated with an increase in hospital admissions and pulmonary exacerbations (PEs), and a 3-fold increase in the risk of death compared to NCFBE patients without PA.[2]
- Inhaled antibiotics and recombinant human DNase have been successfully developed for the prevention of PEs in cystic fibrosis (CF) patients colonized with PA but 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 NCFBE 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 two identical phase III trials (ORBIT-3 and ORBIT-4) in adult patients with CT-scan documented NCFBE who have chronic lung infections with PA.
- The placebo controlled Phase 2b study ORBIT-2, using the same dose 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 134 days).[3] The summary of AEs indicated similarities of AEs and SAEs in the two treatment groups but a favorable pulmonary AE profile in the ARD-3150 group compared to placebo.

METHODS

Major Study 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 nonresistant to ciprofloxacin.
- Patients with active non-TB mycobacterial infections are included as long as they are not currently being treated wit an antibiotic.
- Patients on chronic macrolide treatment at baseline are included.

Study Design and Assessments

- Each trial has a 48-week double blind period of 6 cycles of 28 days on and 28 days off treatment comparing ARD-3150 against 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-B, respiratory domain) during the double blind phase.
- Other endpoints include microbiology assessments (PA density, ciprofloxacin MIC for PA, isolation and quantification of other selected pathogens, PA sensitivity testing to selected antibiotics), 6 minute walk test and productivity questions.
- Spirometry, DLCO and adverse events are monitored as safety indicators.
- Each observed worsening of enrolled patients is rigorously assessed for the occurrence of a PE based on protocol specified distinct symptoms, signs, or laboratory findings and an adjudication committee.[4]
- Pharmacokinetic assessments include ciprofloxacin concentrations in blood and sputum at 2 time points during the study, and a pharmacokinetic profile sub-study conducted during the Open Label Extension phase of the ORBIT 3 study.

Definition of Pulmonary Exacerbation (PE)

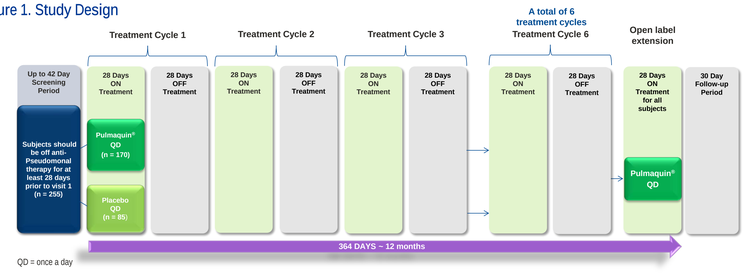
The Investigator will evaluate patients for protocol-defined PEs throughout the study according to the following criteria:

- A PE is defined by the presence of specific abnormal respiratory signs or symptoms with an onset date and an end date. An abnormality is a change from the patient's baseline in the following symptoms, signs, or laboratory findings.[4]
  - Change in sputum production (consistency, color, volume, or hemoptysis)
  - Increased dyspnea (chest congestion or shortness of breath)
  - Increased cough
  - **Fever (≥ 38°C)**
  - Increased wheezing
  - Decreased exercise tolerance, malaise, fatigue, or lethargy
  - FEV1 or FVC decreased 10% from a previously recorded value
  - Radiographic changes indicative of a new pulmonary process
  - Changes in chest sounds
- The onset date of a PE is defined as the first point at which 4 or more abnormalities from the list above occur concurrently in a patient at once.
- The end date of the PE is defined based on the Investigator's judgment of resolution or the conclusion of treatment with antibiotics (if antibiotics were used to treat the pulmonary exacerbation), whichever occurs later and regardless of the number of different consecutive antibiotic treatments required.
- The severity of pulmonary exacerbations is defined as follows:
  - Mild: Adjustments in treatment, including increase in frequency of current therapy, but excluding use of antibiotics or no increase in the dose of macrolides.
  - Moderate: Treatment with oral or inhaled antibiotics, or increase in the dose of macrolides.
  - Severe: Treatment with intravenous antibiotics and/or hospitalization.

Quality of Life-Bronchiectasis (QOL-B) Outcome Measure

- The Quality of Life instrument used in ORBIT-3 and -4 is the QOL-B, Version 3.1 outcome measure that has been specifically designed and assessed for NCFBE patients. The QOL-B is the only patient-reported outcome measure developed specifically with input from patients with bronchiectasis and medical experts in bronchiectasis, and has been recently validated in two clinical trials with an inhaled antibiotic in NCFBE patients.[5]
- The QOL-B is a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related QOL for patients with NCFBE.
  - It contains 37 items on 8 scales (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden).
  - It is developed per the Food and Drug Administration guidance , and the European Medicines Agency Reflection Paper.
- 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.

Figure 1. Study Design



RESULTS

Overview of Patient Enrollment

- 1047 patients were screened in the U.S., Canada, Australia, New Zealand, Israel, South Korea, Taiwan, South Africa, U.K., Germany, France, Spain, Italy, Ireland, Georgia, Serbia, Poland, Romania, Latvia and Peru.
- Both trials were fully enrolled in September 2015 with a total of 582 patients dosed, and the topline data is expected in 2016.

Table 1. Overview of Orbit 3&4 Studies – Subject Enrollment by Region

Participant Status	Asia Pacific	North America	Western Europe	Central & Eastern Europe	Africa & South America	Total
Screened	208	215	384	181	59	1047
Non-eligible	68	105	180	73	23	449
Randomized	140	110	204	108	36	598
Treated	137	105	198	107	35	582
Screen Failure Rate	33%	49%	47%	40%	39%	43%

Asia Pacific: Australia, New Zealand, South Korea, Taiwan
North America: US, Canada
Western Europe: France, Germany, Ireland, Italy, Spain, UK, Israel
Central & Eastern Europe: Hungary, Romania, Serbia, Poland, Georgia, Latvia
Africa & South America: South Africa, Peru

SUMMARY AND CONCLUSIONS

- The two well-controlled clinical trials ORBIT-3 and -4 will provide a large database of well-defined NCFBE patients with chronic PA colonization to investigate the effect of ARD-3150 on the prevention of PEs using a rigorous definition of exacerbation.
- Assessments of microbiology, quality of life, PK analysis and other endpoints will provide a comprehensive analysis of the benefit of ARD-3150.
- The open label extension with 28-day ARD-3150 treatment will provide additional information on the safety and effect of inhaled ARD-3150 for the management of patients with NCFBE colonized with PA.

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GRIFOLS