Inhaled Liposomal Ciprofloxacin in Patients With Bronchiectasis and Chronic *Pseudomonas aeruginosa* Infection: Results From Two Parallel Phase III Trials (ORBIT-3 and ORBIT-4)

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INTRODUCTION

- Patients with non-cystic fibrosis bronchiectasis (NCFBE) and *Pseudomonas aeruginosa* (PA) infection have a greater risk of frequent pulmonary exacerbations (PEs), hospital admissions, decreased quality of life, and higher mortality[1,2]
- ARD-3150 is a once-daily inhaled antibiotic containing liposome-encapsulated ciprofloxacin 150 mg/3 mL and free ciprofloxacin 60 mg/3 mL[3]
- ORBIT-3 and ORBIT-4 were identical, 48-week, multinational, randomized, double-blind, placebo-controlled phase III trials in patients with NCFBE and chronic PA lung infections

OBJECTIVES

- These trials were designed to evaluate the efficacy of once-daily ARD-3150
  - In delaying time to first exacerbation
  - In decreasing the frequency of PEs

METHODS

Patients

- Patients ≥18 years with a confirmed diagnosis of NCFBE by computed tomography and ≥2 PEs treated with antibiotics in the preceding 12 months
- Key inclusion criteria
  - Documented history of chronic lung infection with PA and presence of ≥1 nonresistant PA isolate at screening
  - FEV_1 (forced expiratory volume in 1 second) ≥25% of predicted values at the screening visit
  - Stable respiratory disease at randomization
- Key exclusion criteria
  - Clinical diagnosis of cystic fibrosis
  - Primary diagnosis of chronic obstructive pulmonary disease related to smoking history of >10 cigarette pack-years
  - Non-tuberculosis mycobacterial infection requiring treatment
  - Active tuberculosis
  - PE during screening requiring treatment with inhaled, oral, or intravenous antibiotics
  - Intravenous, oral, or inhaled antipseudomonal antibiotics (except chronic macrolides) within 28 days of randomization

Study Design

- Nebulized ARD-3150 or placebo (randomized 2:1) were administered once daily for 6 cycles of 28 days on treatment, separated by 28 days off treatment, during the 48-week double-blind phase

Protocol Definitions for Determining a PE

- New/change in signs/symptoms:
  - Change in sputum production (consistency, color, volume, or hemoptysis)
  - Increased dyspnea (chest congestion, shortness of breath), cough, fever (≥38ºC), or wheezing
  - Decreased exercise tolerance, malaise, fatigue, or lethargy
  - FEV_1 or forced vital capacity decreased 10% from a previously recorded value
  - Radiographic changes indicative of a new pulmonary process and changes in chest sounds
- Time of PE onset was when ≥4 signs or symptoms occurred concurrently

PE Severity

- *Mild*: Adjustments in treatment, including increase in frequency of current therapy, but excluding the 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
- When the investigator's assessment was in disagreement with the protocol definitions, a review was performed by a blinded adjudication committee

RESULTS

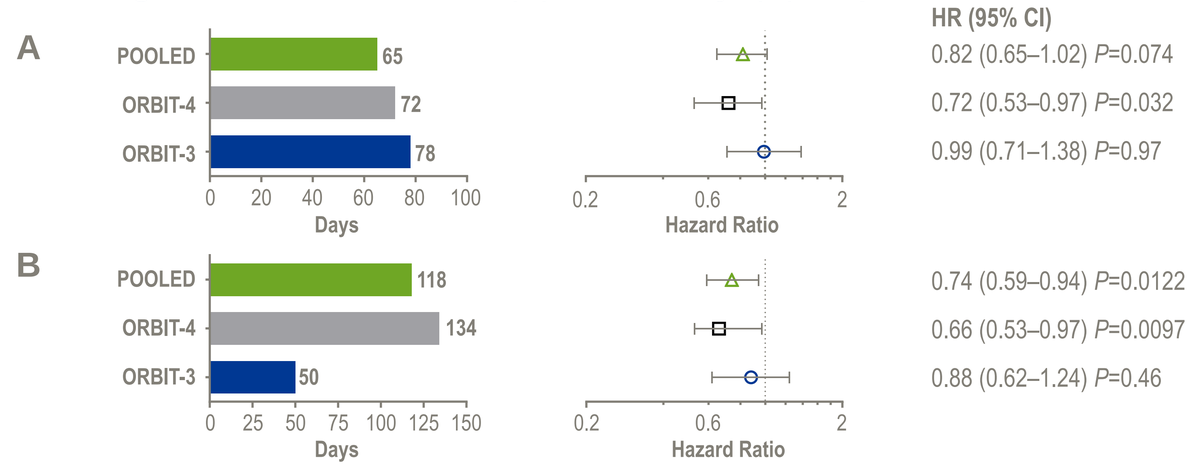
- In ORBIT-3, a total of 514 patients were screened and in ORBIT-4, a total of 533 patients were screened
- Baseline demographics are shown in **Table 1**

Table 1. Baseline demographics

Characteristic	ORBIT-3		ORBIT-4	
	ARD-3150 (n=183)	Placebo (n=95)	ARD-3150 (n=206)	Placebo (n=98)
Age (years), mean ± SD	64±14	67±11	63±13	64±13
Race, n (%)				
White	161 (88)	89 (94)	168 (82)	82 (84)
Asian	15 (8)	4 (4)	11 (5)	4 (4)
Black	3 (2)	1 (1)	2 (1)	1 (1)
Other	4 (2)	1 (1)	25 (12)	11 (11)
Ethnicity, n (%)				
Hispanic or Latino	6 (3)	3 (3)	25 (12)	9 (9)
Nonsmoker, n (%)	180 (98)	94 (99)	204 (99)	98 (100)
Baseline FEV_1 % predicted[a], mean ± SD	57±22	57±20	63±22	60±21
Number of PEs treated with antibiotics in 12 months prior to screening, n (%)				
2–3	141 (77)	69 (73)	167 (81)	76 (78)
4–7	39 (21)	25 (26)	38 (18)	18 (18)
>7	3 (2)	0	2 (1)	3 (3)

[a] n for FEV_1 for ORBIT-3 ARD-3150 = 183, placebo = 95; for ORBIT-4 ARD-3150 = 205, placebo = 98
SD, standard deviation; FEV_1, forced expiratory volume in 1 second; PE, pulmonary exacerbation

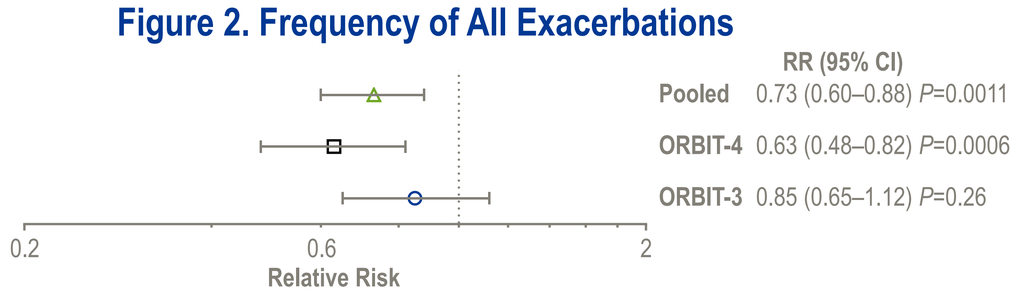
Figure 1. Time to First PE: (A) All Severity; (B) Required Antibiotics



PE, pulmonary exacerbation; HR, hazard ratio; CI, confidence interval

- ARD-3150 significantly increased median time to first PE (all severities) in ORBIT-4 (**Figure 1A**)
- ARD-3150 significantly increased median time to first PE that required treatment with antibiotics in ORBIT-4 and the pooled analysis (**Figure 1B**)

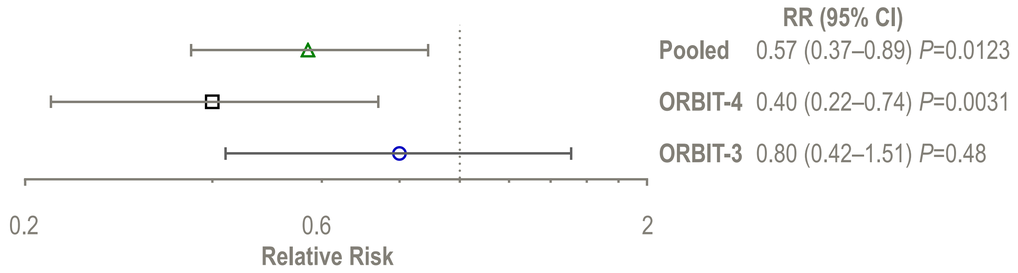
Figure 2. Frequency of All Exacerbations



Stratified negative binomial regression; stratified by sex and prior pulmonary exacerbations. RR, relative risk

- ARD-3150 was associated with a significant reduction in the point estimate of the annual frequency of PEs in ORBIT-4 and in the pooled analysis (**Figure 2**)

Figure 3. Frequency of Severe Exacerbations



Stratified negative binomial regression; stratified by sex and prior pulmonary exacerbations. RR, relative risk

- ARD-3150 was associated with a significant reduction in the point estimate of the annual frequency of severe PEs in ORBIT-4 and in the pooled analysis (**Figure 3**)

Table 2. Adverse events

N (%)	ORBIT-3		ORBIT-4	
	ARD-3150 (N=183)	Placebo (N=95)	ARD-3150 (N=206)	Placebo (N=98)
TEAE / TEAE related to study drug	164 (90%) / 78 (43%)	87 (92%) / 32 (34%)	178 (86%) / 58 (28%)	95 (97%) / 34 (35%)
SAE / SAE related to study drug	56 (31%) / 6 (3%)	24 (25%) / 1 (1%)	35 (17%) / 1 (0.5%)	28 (28%) / 1 (1%)
Discontinued due to TEAE	16 (9%)	3 (3%)	5 (2%)	4 (4%)
Death[a]	5 (3%)	3 (3%)	1 (0.5%)	2 (2%)
AEs related to study drug reported in ≥5% of patients				
Cough	24 (13%)	16 (17%)	18 (9%)	10 (10%)
Dyspnea	14 (8%)	7 (7%)	11 (5%)	6 (6%)
Wheezing	10 (6%)	7 (7%)	10 (5%)	3 (3%)
Other AE of interest				
Bronchospasm/bronchial hyper-reactivity	4 (2%)	1 (1%)	1 (0.5%)	1 (1%)

[a] No deaths were considered related to study drug
TEAE, treatment-emergent adverse event; SAE, serious adverse event; AE, adverse event

CONCLUSIONS

In patients with NCFBE, PA and ≥2 PEs in the year preceding enrollment, ARD-3150	ORBIT-3	ORBIT-4	Pooled analysis
Increased the median time to first PE (all severities)	NS	✓	NS
Increased the median time to first PE requiring treatment with antibiotics	NS	✓	✓
Reduced the frequency of all PEs regardless of severity	NS	✓	✓

Not significant (NS); ✓ denotes statistical significance

- ARD-3150 was well tolerated with a similar adverse event profile to placebo

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