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

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Background

- 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
  - Higher mortality

- ARD-3150 is a once-daily inhaled antibiotic containing liposome encapsulated ciprofloxacin 150 mg/3 mL and free ciprofloxacin 60 mg/3 mL

- Administered through the PARI LC® Sprint nebulizer

Chalmers et al, AJRCCM 2014; Finch et al, Ann Am Thorac Soc 2015; Serisier et al, Thorax 2013

Background

- 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, followed by a 28-day open-label extension

- 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

ORBIT-3 & ORBIT-4 Clinical Site Countries

Methods – Patients

Patients ≥18 years with a confirmed diagnosis of NCFBE by CT and at least 2 PEs treated with antibiotics in the preceding 12 months

Key Inclusion Criteria

- CT-confirmed diagnosis of bronchiectasis
- Documented history of at least 2 PEs treated with antibiotics within the previous 12 months
- Documented history of chronic lung infection with PA and presence of at least 1 nonresistant PA isolate at the screening visit
- FEV_1 ≥25% predicted at the screening visit
- Stable respiratory disease at randomization

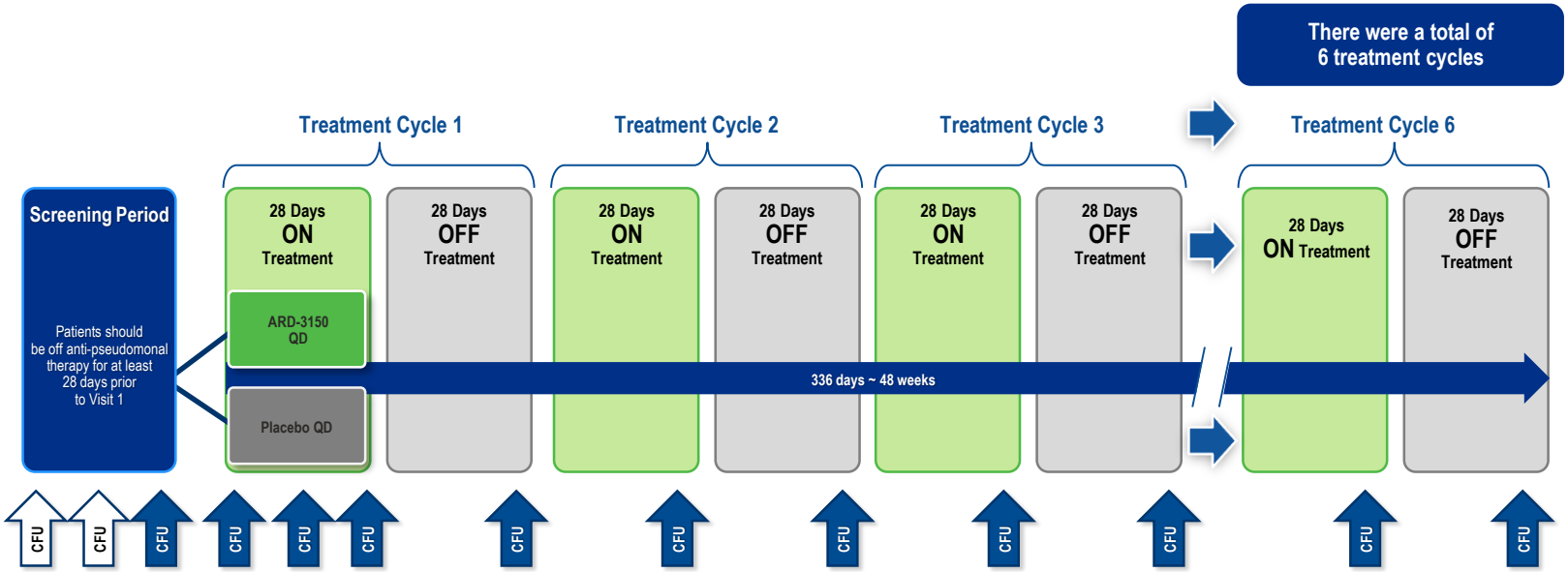
Key Exclusion Criteria

- Clinical diagnosis of cystic fibrosis
- Primary diagnosis of COPD and smoking history of >10 cigarette pack-years
- NTM 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

CT, computed tomography; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; NTM, non-tuberculosis mycobacterial

Study Design – ORBIT-3 and ORBIT-4

Nebulized ARD-3150 or placebo 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



CFU, colony forming units of *P. aeruginosa*, determined from sputum analysis
QD, once daily

Protocol Definitions for Determining PE

Pulmonary Exacerbation

New/change in signs or symptoms:

- Change in sputum consistency, color, volume, or hemoptysis
- Increased dyspnea (chest congestion or shortness of breath)
- Increased cough
- Fever (≥38ºC)
- Increased wheezing
- Decreased exercise tolerance, malaise, fatigue, or lethargy
- FEV_1 or FVC decreased 10% from a previous value
- Radiographic changes indicative of a new pulmonary process
- Changes in chest sounds

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

Time of PE onset was when ≥4 signs or symptoms occurred concurrently

Pulmonary Exacerbation Blinded Adjudication Committee

- Blinded adjudication of PEs when the investigator's assessment was in disagreement with the protocol definitions

*O'Donnell et al. 1998
FVC, forced vital capacity

Baseline Demographics

	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 or African American	3 (2)	1 (1)	2 (1)	1 (1)
Other / Not Reported	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*, mean ± SD	57 ± 22	57 ± 20	63 ± 22	60 ± 21
Number of PEs, 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)

*n for FEV_1 for ORBIT-3: ARD-3150 = 183, placebo = 95; for ORBIT-4: ARD-3150 = 205, placebo = 98
SD, standard deviation; FA population

Disposition / Withdrawals From Study

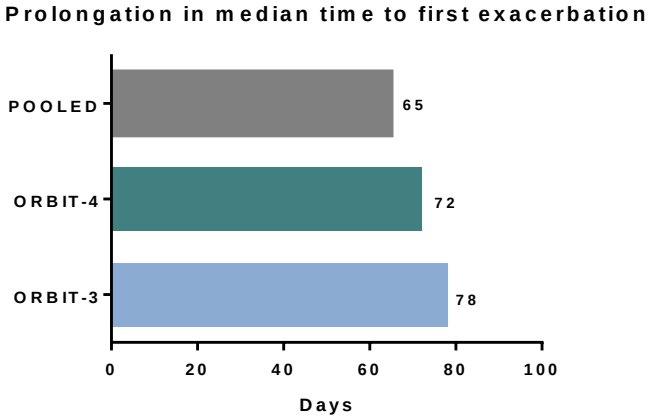
	ORBIT-3 Screened = 514		ORBIT-4 Screened = 533	
	ARD-3150	Placebo	ARD-3150	Placebo
Randomized, n	183	95	206	98
Withdrawn, n (%)	41 (22)	18 (19)	28 (14)	17 (17)
Reason for withdrawal, n (%)				
Adverse event	16 (9)	3 (3)	5 (2)	4 (4)
Per-protocol defined PE	1 (0.5)	0	0	0
Lack of efficacy	2 (1)	0	1 (0.5)	0
Lost to follow-up	3 (2)	1 (1)	3 (2)	0
Investigator decision	3 (2)	1 (1)	3 (2)	1 (1)
Protocol deviation	2 (1)	1 (1)	1 (0.5)	1 (1)
Withdrawal by subject	14 (8)	11 (12)	13 (6)	11 (11)
Other	0	1 (1)	2 (1)	0
Died*, n (%)	5 (3)	3 (3)	2 (1)	4 (4)
Completed double-blind period, n (%)	142 (78)	77 (81)	178 (86)	81 (83)

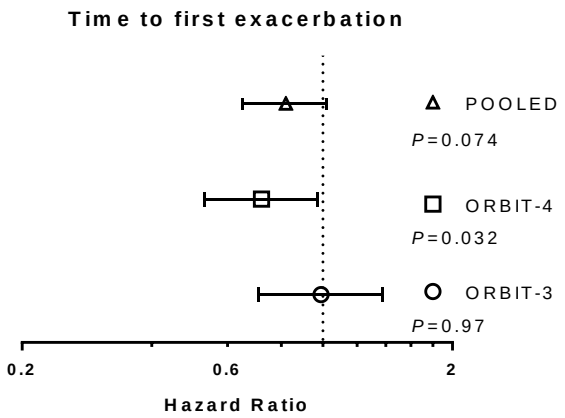
* One subject in ORBIT-3 died after enrollment during screening, prior to randomization/dosing

FA population

Time to First PE - all severities

ARD-3150 significantly increased median time to first PE (all severities) in ORBIT-4



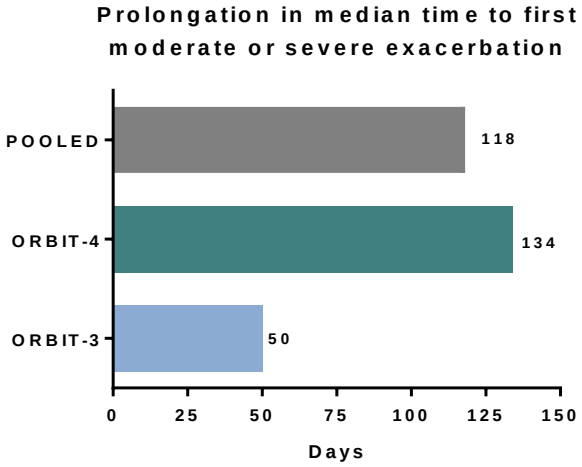


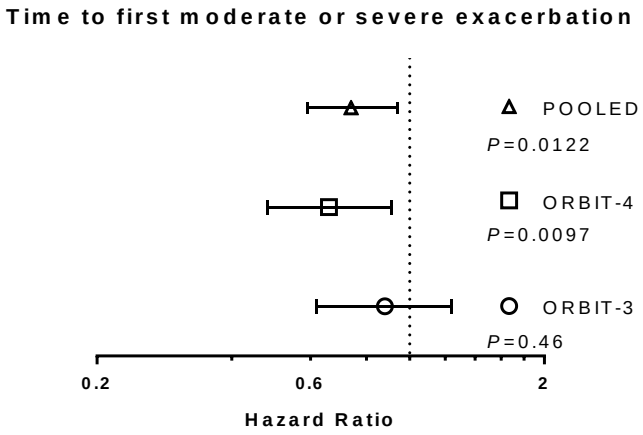
	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit
POOLED	0.82	0.65	1.02
ORBIT-4	0.72	0.53	0.97
ORBIT-3	0.99	0.71	1.38

Stratified unweighted log-rank test
Stratification factors: sex and previous number of exacerbations in the past 12 months prior to randomization

Time to First Moderate or Severe PE

ARD-3150 significantly increased median time to first PE that required treatment with antibiotics in ORBIT-4 and the pooled data analysis



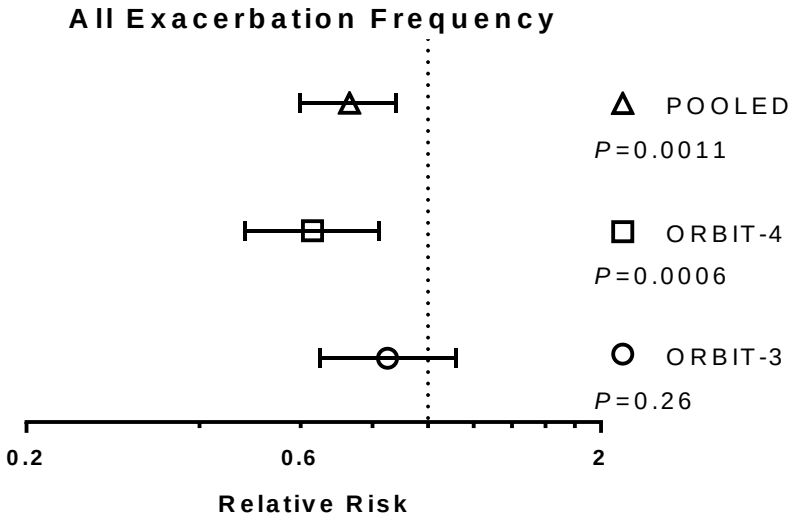


	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit
POOLED	0.74	0.59	0.94
ORBIT-4	0.66	0.48	0.91
ORBIT-3	0.88	0.62	1.24

Stratified unweighted log-rank test
Stratification factors: sex and previous number of exacerbations in the past 12 months prior to randomization

Frequency of all PEs

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

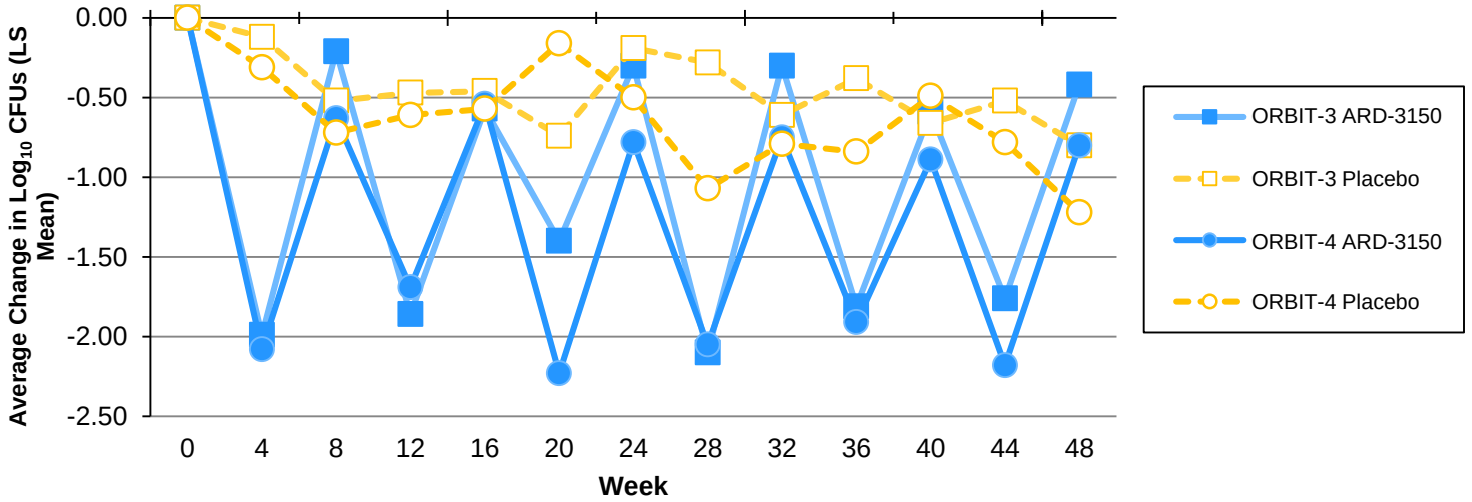


	Relative Risk	Lower Confidence Limit	Upper Confidence Limit
POOLED	0.73	0.60	0.88
ORBIT-4	0.63	0.48	0.82
ORBIT-3	0.85	0.65	1.12

Stratified negative binomial regression; stratified by sex and prior PEs

Change in Sputum Density of *P. aeruginosa*

ARD-3150 significantly reduced sputum density of *P. aeruginosa* while on treatment over the 48-week period



With the exception of 1 visit in ORBIT-3, statistically significant reductions were observed at the end of every on-treatment period throughout the course of both studies

Adverse Events

N (%)	ORBIT-3		ORBIT-4	
	ARD-3150 (N=183)	Placebo (N=95)	ARD-3150 (N=206)	Placebo (N=98)
TEAE / Related to study drug	164 (90%) / 78 (43%)	87 (92%) / 32 (34%)	178 (86%) / 58 (28%)	95 (97%) / 34 (35%)
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%)
TEAEs leading to Death*	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%)

- There were no significant differences in changes in FEV_1 % predicted, FVC, or DLCO at week 48 between the ARD-3150 and placebo groups in ORBIT-3 and ORBIT-4

* No deaths were considered related to study drug

AE, adverse event; DLCO, diffusing capacity of the lungs for carbon monoxide; TEAE, treatment-emergent adverse event; SAE, serious adverse event

Conclusions

In patients with NCFBE, PA and ≥2 exacerbations in the year preceding enrollment, ARD-3150:

	ORBIT-3	ORBIT-4	POOLED ANALYSIS
Increased the median time to first PE (all severities)	**NS**	✓	**NS**
Reduced the frequency of all PEs regardless of severity	**NS**	✓	✓
Increased the median time to first PE requiring treatment with antibiotics	**NS**	✓	✓
Reduced sputum density of PA without attenuation of antibiotic activity during each treatment cycle over the 48-week trial	✓	✓	✓

Not significant (NS); ✓ denotes statistical significance

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