Reduction in Frequency of Pulmonary Exacerbations With Inhaled ARD-3150 in Non-Cystic Fibrosis Bronchiectasis (NCFB) Patients is Independent of *Pseudomonas aeruginosa* Susceptibility at Baseline

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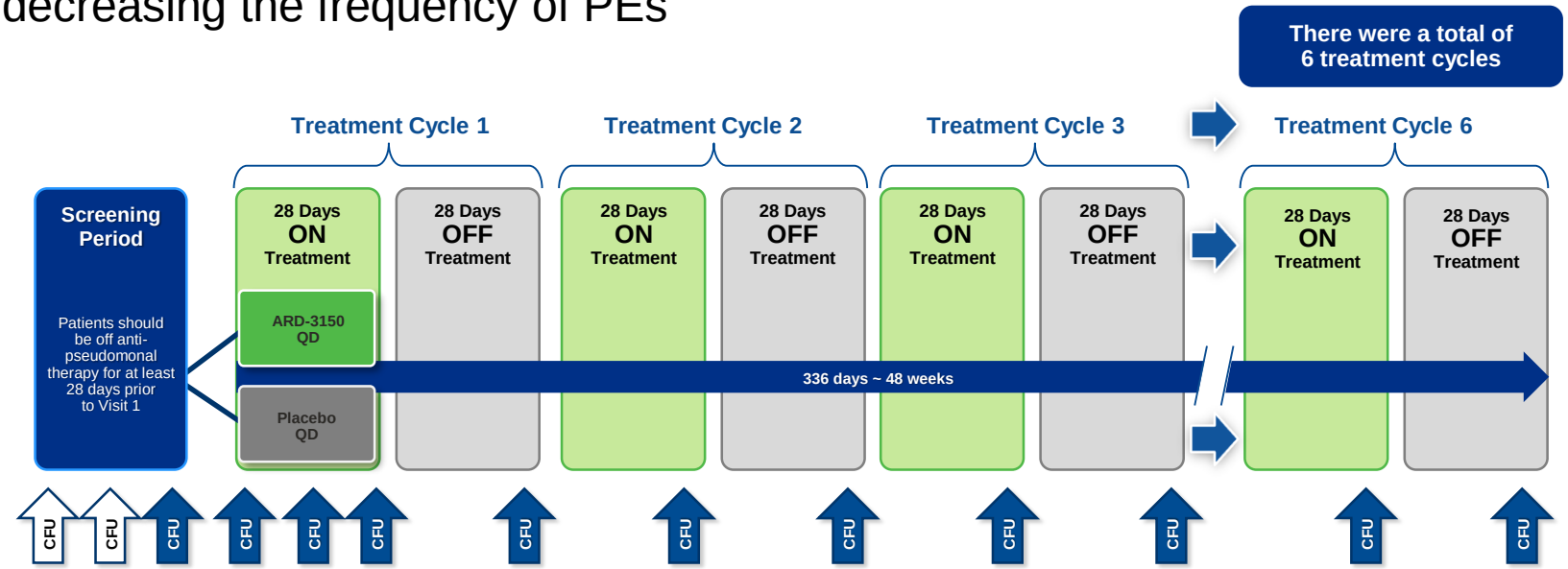
Introduction

- Patients with NCFB are often chronically infected with *Pseudomonas aeruginosa* (PA), requiring multiple courses of oral and iv antibiotics including quinolones for pulmonary exacerbations (PEs)
  - Repeated antibiotic treatment of PEs often results in resistant PA isolates from sputum
- Inhaled administration of antibiotics can produce localized high concentrations within the airway and minimize systemic exposure
- ARD-3150 is a once-daily inhaled antibiotic containing liposome encapsulated ciprofloxacin 150 mg/3 mL and free ciprofloxacin 60 mg/3 mL[1]

[1]Serisier et al, Thorax 2013

ORBIT-3 (ARD-1201) and ORBIT-4 (ARD-1202): Study Design

The primary endpoints were to evaluate ARD-3150 vs placebo in
- delaying time to first exacerbation
- decreasing the frequency of PEs



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

Methods – Patients

Patients ≥18 years with a confirmed diagnosis of NCFB 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

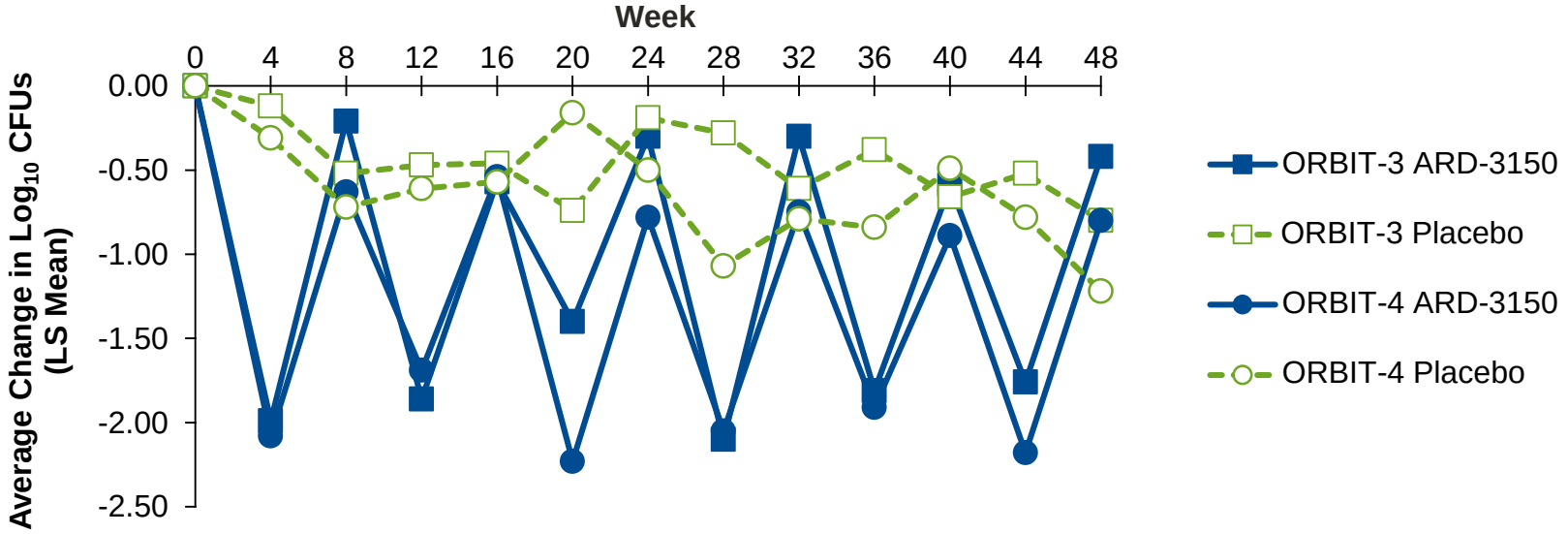
- Clinical diagnosis of cystic fibrosis
- Primary diagnosis of COPD and smoking history of >10 cigarette pack-years
- NTM infection requiring treatment
- Active tuberculosis
- PE during screening requiring treatment with inhaled, oral, or intravenous antibiotics
- Intravenous, oral, or inhaled antipseudomonal 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

**** Did not exclude subjects who had also resistant isolates***

Change in Sputum Density of *P. aeruginosa*

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

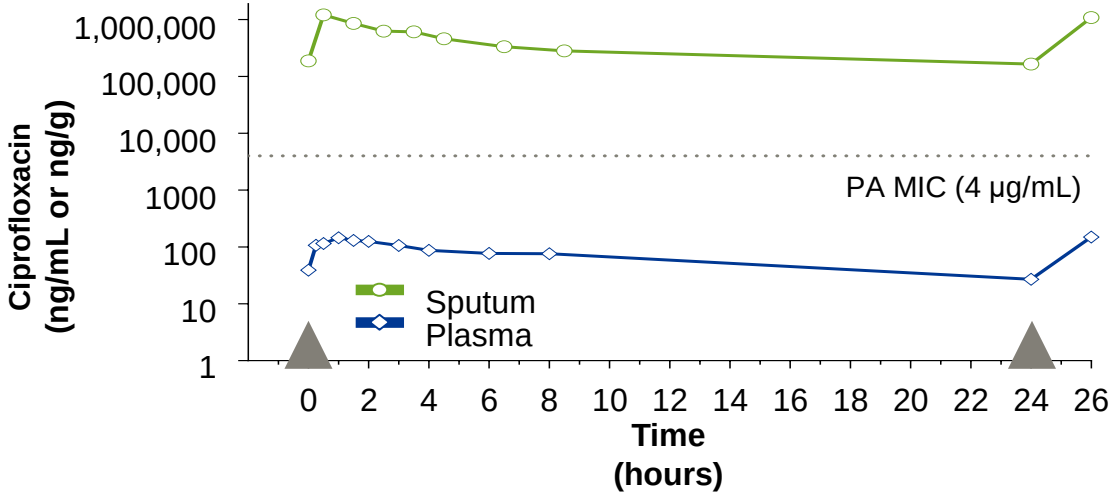


With the exception of 1 visit in ORBIT-3, statistically significant reductions were observed at the end of every on-treatment period throughout the course of both studies

PA, *Pseudomonas aeruginosa*; CFU, colony-forming units; LS, least squares

ARD-3150 Concentrations: Sputum and Plasma

- In a pharmacokinetic sub study from ORBIT-3, we determined the sputum and plasma concentrations of ciprofloxacin during treatment with ARD-3150
- Substantially higher concentrations of ciprofloxacin were observed in sputum than in plasma



Analysis is shown for Day 7 at just before dosing (arrow) with ARD-3150 treatment through 2 hours after the next inhalation event (arrow) on Day 8
PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

Analysis of PA Susceptibility vs PE frequency

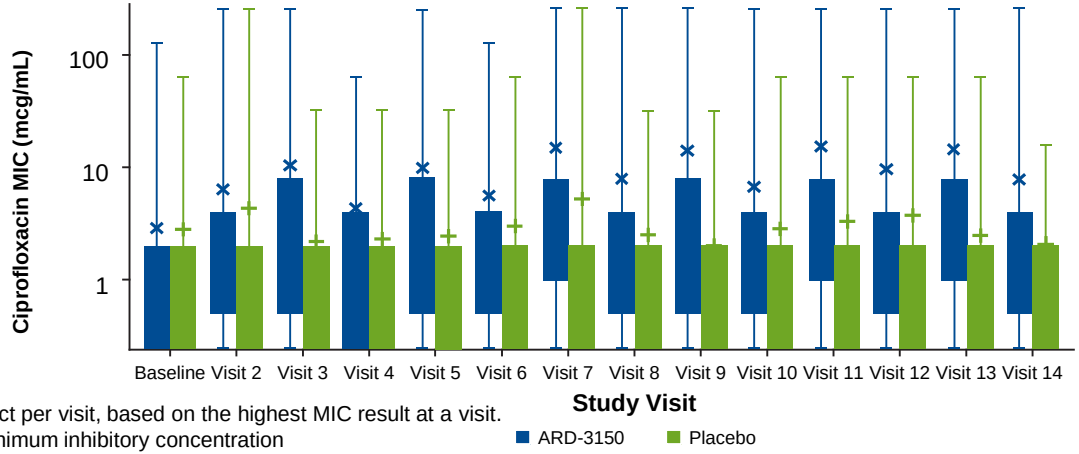
- In a post-hoc analysis, we sought to determine whether baseline susceptibility of PA isolates to ciprofloxacin or emergence of resistance during the trial influenced the frequency of PEs in NCFB patients treated with ARD-3150 when compared to the frequency of PEs in the same patients observed in the year prior to study entry
  - Resistant PA isolates were defined as having a minimum inhibitory concentration (MIC) ≥4 mcg/mL for ciprofloxacin
  - Because sputum concentrations of ciprofloxacin following inhalation of ARD-3150 are much higher than those achieved with oral or IV therapy, the conventional definition of resistance may be irrelevant for clinical efficacy

PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

Methods

- Ciprofloxacin minimum inhibitory concentration (MIC) was evaluated in ARD-3150 treated patients at baseline and at each treatment interval
- Placebo treatment was not included in this post-hoc analysis, as the ciprofloxacin MIC in placebo treated patients did not vary over the course of the study

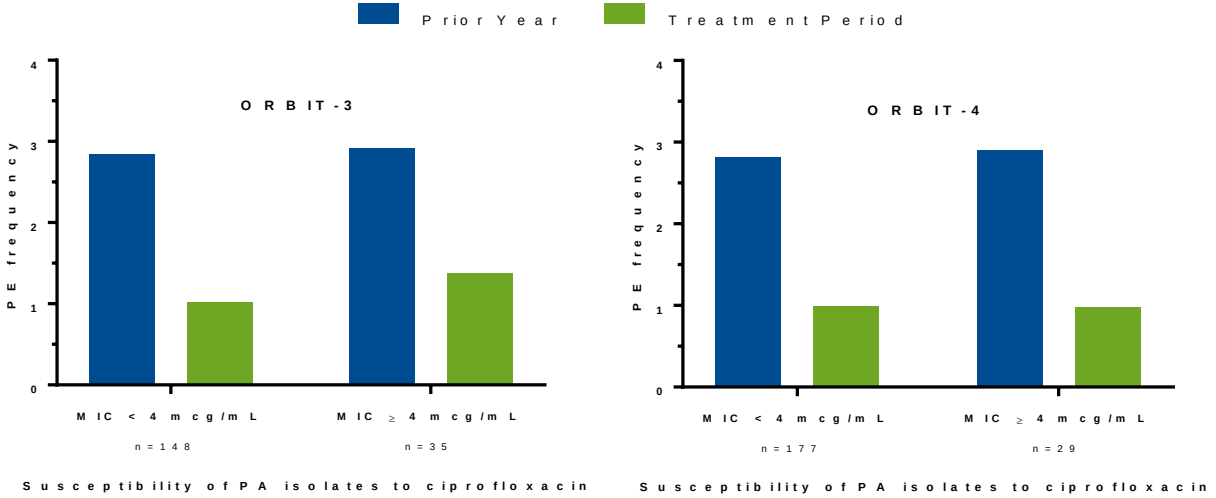
Highest ciprofloxacin MIC for PA isolates by visit (pooled ORBIT-3 and ORBIT-4)



Includes data from one isolate per subject per visit, based on the highest MIC result at a visit.
PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

Frequency of PEs in Patients With and Without Resistant Isolates of PA During the Double Blind Period

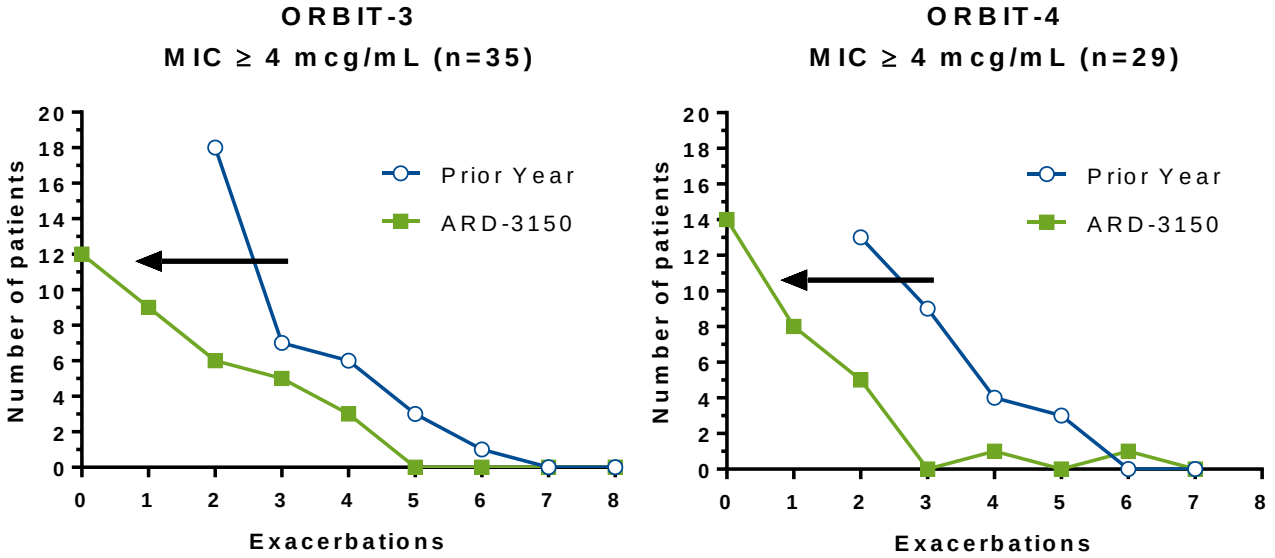
- ARD-3150 treatment decreased PE frequency similarly in patients with and without resistant isolates at study entry



PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

Reduction in Exacerbations in Patients With Resistant Isolates of PA

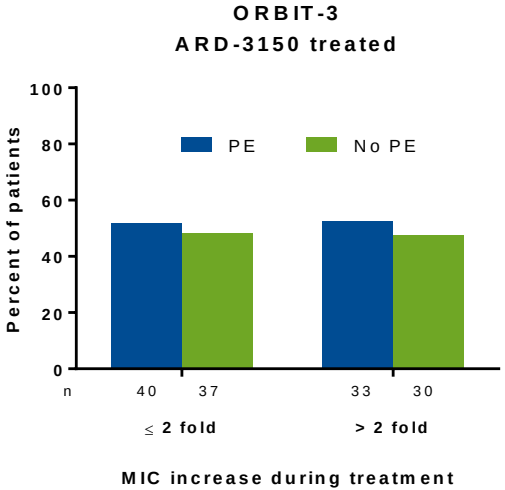
- Treatment with ARD-3150 reduced the number of PEs compared with the prior year in patients with resistant isolates at baseline (MIC≥ 4 mcg/mL), shifting the exacerbation distribution curve to the left (arrow)

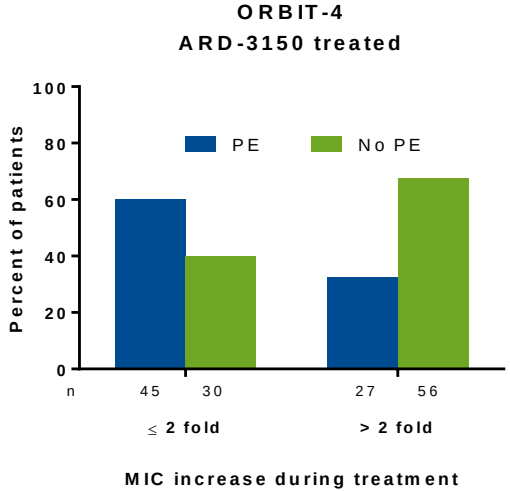


PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

No Evidence that an Increase in MIC During Treatment Adversely Impacted PE Frequency

- Patients were stratified based on whether or not PA MIC increased from baseline over the course of the 48 week study
- An increase in MIC of ciprofloxacin (>2-fold) over the course of the 48-week study was not associated with an increased likelihood of having a PE





PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

Conclusions

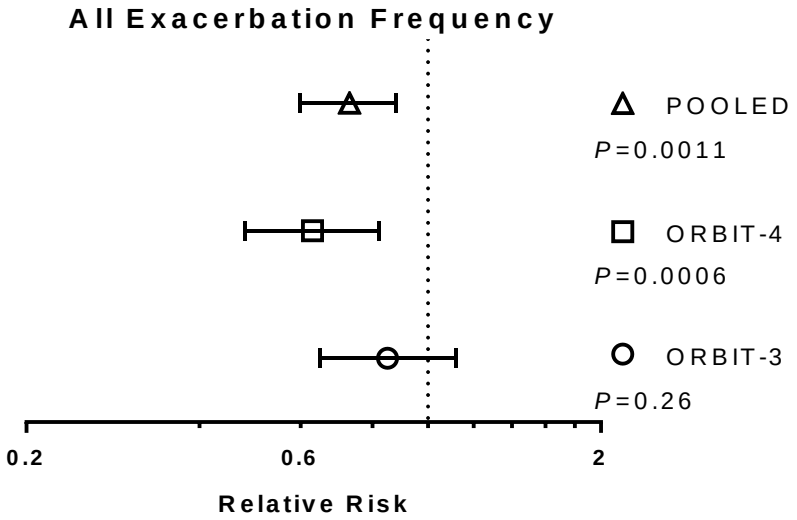
- Ciprofloxacin concentrations following once daily administration of ARD-3150 remained high during the on-treatment periods
- There was a sustained antipseudomonal effect during every on-treatment period for 48 weeks
- The observed impact of once-daily inhaled ARD-3150 on PE frequency during the 48-week treatment period was similar, regardless of PA susceptibility to ciprofloxacin at baseline
- There was no evidence that an increase in MIC over the course of the study negatively influenced the effect of ARD-3150 on PE frequency

PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

Backup

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

Pharmacokinetic Parameters of ARD-3150 in Plasma and Sputum

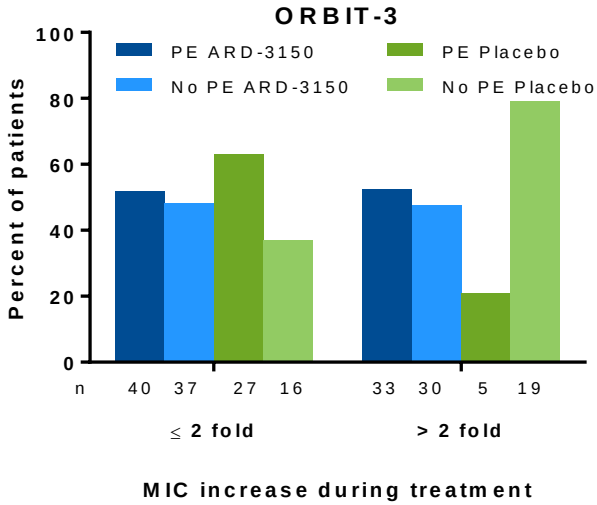
Statistic	C_{min} (ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}tau}$ (h*ng/mL)	$t_{½}$ (h)	CL/F_{ss} (L/h)
Plasma	n					
N	15	15	15	15	6	15
Median value	26.00	180.0	1.370	1481	9.324	127.6
Mean (CV%)	41.27 (148.8)	195.0 (59.4)	1.645 (88.4)	2034 (93.2)	9.22 (12.6)	175.9 (109.4)
Statistic	C_{min} (ng/g)	C_{max} (ng/g)	T_{max} (h)	$AUC_{0\text{-}tau}$ (h*ng/g)		
Sputum						
N	16	16	16	15		
Median value	70,250	1,530,000	0.750	11,570,000	-	-
Mean (CV%)	167,600 (125.9)	2,193,000 (86.5)	1.639 (98.6)	17,500,000 (90.9)	-	-

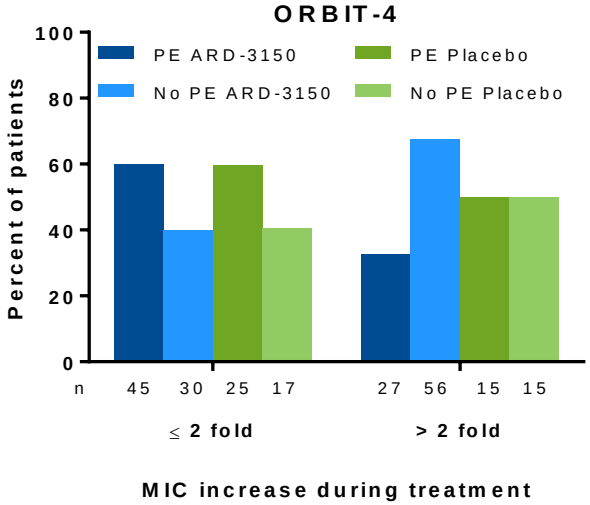
Pharmacokinetic parameters determined using Phoenix WinNonLin 6.3 (Certara, Princeton, NJ, USA). Due to the variable nature of the sputum concentration data over the dosing interval within each individual, a terminal elimination phase could not be easily identified for the majority of subjects.

C_{min}, minimum concentration; C_{max}, maximum concentration; T_{max}, time to maximum concentration; $AUC_{0\text{-}tau}$, area under the concentration-time curve from time 0 to end of dosing period; $t_{1/2}$, half-life; CL/F_{ss}, oral clearance at steady state; CV%, coefficient of variation

No Evidence that an Increase in MIC During Treatment Adversely Impacted PE Frequency in the Linhaliq Group

- Patients were stratified based on whether or not PA MIC increased from baseline over the course of the 48 week study
- An increase in MIC of ciprofloxacin (>2-fold) over the course of the 48-week study was not associated with an increased likelihood of having a PE





PA, *Pseudomonas aeruginosa*; MIC, minimum inhibitory concentration

Results

- At baseline, 19% of ORBIT-3 patients and 14% of ORBIT-4 patients had resistant PA isolates

	ORBIT-3		ORBIT-4	
	MIC < 4 mcg/mL	MIC ≥4 mcg/mL	MIC < 4 mcg/mL	MIC ≥4 mcg/mL
Number of patients	148	35	177	29
Prior year number of PE	421	102	500	84
Prior year per patient PE frequency (mean)	2.84	2.91	2.82	2.90
On treatment number of PE	151	48	174	28
On treatment per patient PE frequency (mean)	1.02	1.37	0.98	0.97
Reduction in per patient PE (mean)	1.82	1.54	1.84	1.93
Patients with an increase in PE on treatment (%)	6.8	5.7	4.5	6.9
Patients with a decrease in PE on treatment (%)	83.7	74.3	81.9	89.7

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