Inhaled Liposomal Ciprofloxacin in Patients With Non-Cystic Fibrosis Bronchiectasis and Chronic *Pseudomonas aeruginosa* Infection: Pharmacokinetics of Once-Daily Inhaled ARD-3150

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INTRODUCTION

- Patients with non-cystic fibrosis bronchiectasis (NCFBE) and *Pseudomonas aeruginosa* (PA) chronic lung 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]
- In the randomized, double-blind, placebo-controlled phase III ORBIT-3 trial, ARD-3150 was investigated in NCFBE patients with chronic lung infections with PA (NCT01515007)
- Treatment with ARD-3150 or placebo consisted of 6 cycles of 28 days on/28 days off treatment, followed by a 28 day open-label extension with once-daily ARD-3150 that included a pharmacokinetic (PK) sub-study

OBJECTIVES

- The PK sub-study was designed to investigate the PK of ciprofloxacin in plasma and sputum mid-way through a 28-day course of inhaled ARD-3150 therapy in patients with NCFBE and chronic PA infection

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 were enrolled in ORBIT-3 (n=278)
- 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

PK Sub-study

- In the open-label extension, nebulized ARD-3150 was administered once-daily for 28 days (PARI LC® Sprint nebulizer) with PK sampling in 16 patients
- Blood was collected pre-dose on Day 7, and at 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, and 8 h post-dose
- Sputum samples were collected pre-dose on Day 7, and 15–30 min, 1–1.5 h, 2–2.5 h, 3–3.5 h, 4–4.5 h, 6–6.5 h, and 8–8.5 h post-dose. If possible, 12-hour samples of sputum and plasma were collected at the study site or at the patient's home
- Additionally, sputum and blood samples were collected pre-dose and 2 hours post-dose on Days 8 and 28
- Plasma and sputum ciprofloxacin PK parameters were determined using non-compartmental analysis
- Accumulation of ciprofloxacin in plasma and sputum was evaluated by the ratio of Day 8 and Day 28 pre-dose and 2-hour post-dose concentrations

Analysis Parameters

- Plasma and sputum ciprofloxacin PK parameters included
  - Area under the concentration-time curve from time 0 to end of dosing period ($AUC_{0\text{-}tau}$)
  - Area under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}\infty}$)
  - Time to maximum concentration (T_{max})
  - Maximum concentration (C_{max})
  - Minimum concentration (C_{min})
  - Half-life ($t_{½}$)
  - Oral clearance at steady state (CL/F_{ss})

RESULTS

- There were 223 plasma and 205 sputum concentrations available for ciprofloxacin analysis
- Median sputum ciprofloxacin PK parameters in plasma and sputum are shown in Table 1
- Median sputum ciprofloxacin C_{max} was 8500 times greater than plasma C_{max}

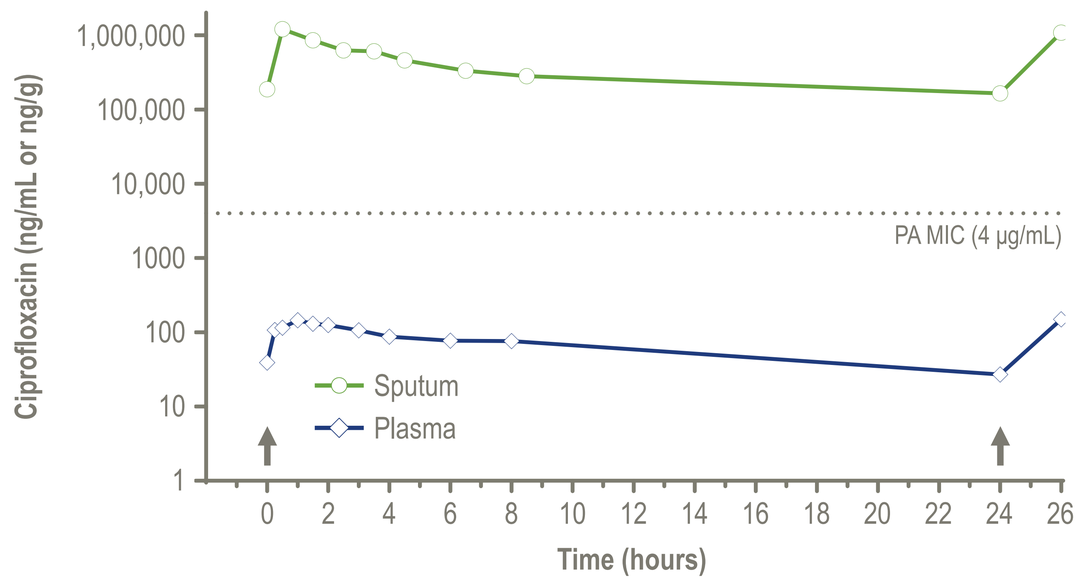
Table 1. ARD-3150 PK parameters in plasma and sputum

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 (PK) 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. CV%, coefficient of variation

- After inhalation of ARD-3150, there was an early peak of free ciprofloxacin both in sputum and plasma, followed by slow elimination (Figure 1)

Figure 1. Pharmacokinetic Profile of ARD-3150 in Sputum and Plasma at Steady State



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

- This profile represents the combined effect of immediate availability of free ciprofloxacin and slow release of the liposome-encapsulated ciprofloxacin from ARD-3150
- There was no systematic trend of further increasing sputum ciprofloxacin concentrations from Day 8 to Day 28, indicating that steady-state levels were sustained
- Median C_{min} of 70.25 µg/g of sputum was much higher than the minimum inhibitory concentration of non-resistant strains of PA for ciprofloxacin (<4 µg/mL)
- Overall, there was no clear systematic trend indicating clinically relevant plasma or sputum ciprofloxacin accumulation from Day 8 to Day 28
  - A highly variable between-subject variability in concentration ratios between Day 8 and Day 28 prevented a robust determination of accumulation

CONCLUSIONS

- Treatment with once-daily inhaled ARD-3150 was associated with high sputum ciprofloxacin concentrations throughout the 24-hour dosing interval, which were several orders of magnitude higher than plasma concentrations
- High sputum concentrations were achieved early after initiation of treatment and remained above the minimum inhibitory concentration of typical PA strains during the 28-day on-treatment period
- Systemic ciprofloxacin concentrations in plasma are at least an order of magnitude lower than plasma concentrations reported in the literature achieved with commonly used therapeutic doses of orally administered ciprofloxacin

REFERENCES

1. Chalmers JD, et al. *Am J Respir Crit Care Med*. 2014;189(5):576–585. 2. Finch S, et al. *Ann Am Thorac Soc*. 2015;12(11):1602–1611. 3. Serisier DJ, et al. *Thorax*. 2013;68(9):812–817.

ACKNOWLEDGMENTS

ORBIT-3 and ORBIT-4 were funded by Aradigm Corporation, Hayward, CA, USA. Medical writing and editorial assistance was provided by Alex Loeb, PhD, Evidence Scientific Solutions, Philadelphia, PA, USA, which was funded by Grifols.

Presented at the 2nd World Bronchiectasis Conference | July 6–8, 2017 | Milan, Italy