# 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 $C_{max}$

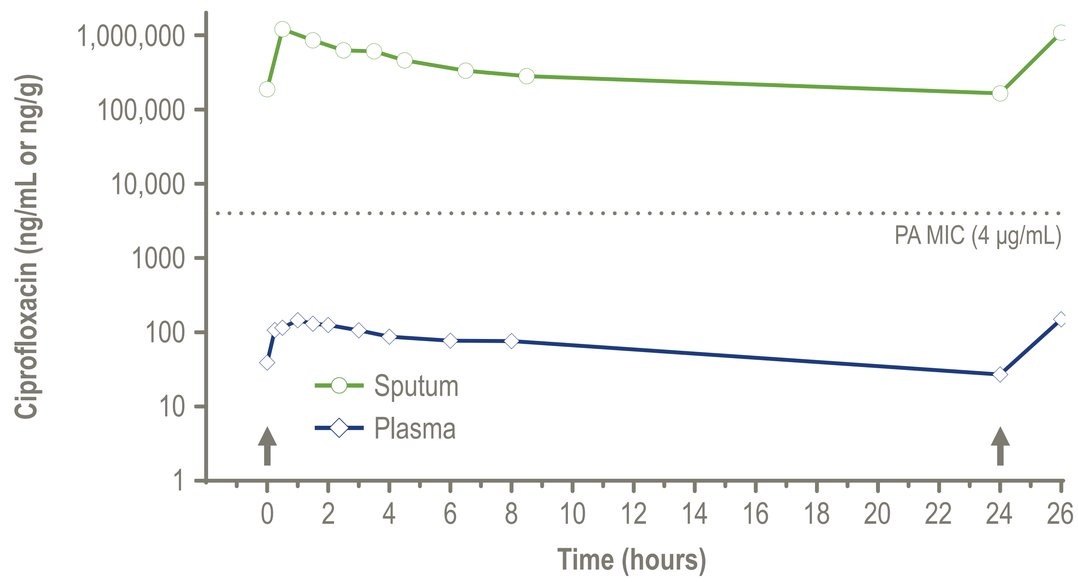
**Table 1. ARD-3150 PK parameters in plasma and sputum**

| 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

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