Dual Release Ciprofloxacin for Inhalation Improves Time to First Exacerbation in Bronchiectasis

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Introduction & Background

Ciprofloxacin is a well-established and extensively utilized broad-spectrum fluoroquinolone antibiotic that is indicated for the treatment of acute lower respiratory tract infections due to *Pseudomonas aeruginosa* (PA). Management of chronic infections and prevention of infectious exacerbations that lead to lung tissue destruction and further decline in lung function would be desirable for long-term quality of life outcomes.

Aradigm developed two aqueous, liposome-encapsulated formulations to increase the concentration and duration of action of ciprofloxacin in the lung: **Ciprofloxacin for Inhalation** (**CFI**) and a **Dual Release CFI** (**DRCFI**). DRCFI provides both a high peak and a sustained release profile of ciprofloxacin in the lungs.

In pre-clinical studies CFI and DRCFI demonstrated efficacy in an animal model of PA lung infections.

In **Cystic Fibrosis (CF)** patients, 14 days of once daily 300 mg **CFI** significantly reduced the mean sputum PA density and pulmonary function results showed a significant (p=0.04) increase in mean absolute FEV_1 of 6.86% from Day 1 to end-of-treatment[1].

In **Bronchiectasis (BE)** patients, once daily 300 mg and 150 mg **CFI** decreased PA CFU by a mean of 4.003 $\log_{10}$ ($p<0.001$) and 3.469 $\log_{10}$ ($p=0.0002$) respectively over the 28-day treatment period[2].

In this poster we highlight results from a 6-month, Phase 2b, randomized double-blind, placebo-controlled trial in 42 **BE** patients (ORBIT-2) who were dosed once-daily with either 210 mg **DRCFI** or placebo for three cycles of 28 days on treatment, followed by 28 days off treatment. A PARI LC Sprint nebulizer and PARI compressor was used to deliver the aerosol in ORBIT-2. Nebulization did not compromise the integrity of the liposomes nor the vesicle size distribution[3].

A second Phase 2b randomized, double blind, placebo-controlled trial in 95 BE patients (ORBIT-1) to evaluate lower doses of CFI has just been completed. Stay tuned!

1. Paul Bruinenberg, Babatunde Otulana, Jim Blanchard, Richard Morishige, David Cipolla, John Wilson, David Serisier. (2008) "The Effect of Once-Daily Inhaled Liposomal Ciprofloxacin Hydrochloride on Sputum Bacterial Density in Cystic Fibrosis Patients with Chronic Pulmonary P. aeruginosa Colonization," Twenty Third Annual North America CF Conference.

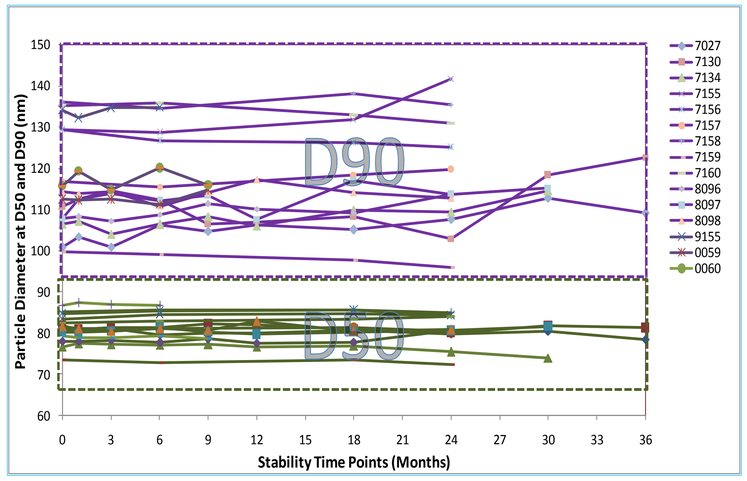
2. Bruinenberg P, Blanchard JD, Cipolla DC, Dayton F, Mudumba S, and Gonda I. (2010) "Inhaled liposomal ciprofloxacin: once a day management of respiratory infections," *Respiratory Drug Delivery 2010*, pp. 73-81. Editors, Richard N. Dalby, Peter R. Byron, Joanne Peart, Julie D. Suman, Stephen J. Farr, Paul M. Young. Davis Healthcare Int'l Publishing, River Grove, IL.

3. Cipolla DC, Dayton F, Fulzele S, Gabatan E, Mudumba S, Yim D, Wu H and Zwolinski R. (2010) "Inhaled Liposomal Ciprofloxacin: In Vitro Properties and Aerosol Performance," *Respiratory Drug Delivery 2010.* pp. 409-414. Editors, Richard N. Dalby, Peter R. Byron, Joanne Peart, Julie D. Suman, Stephen J. Farr, Paul M. Young. Davis Healthcare Int'l Publishing, River Grove, IL.

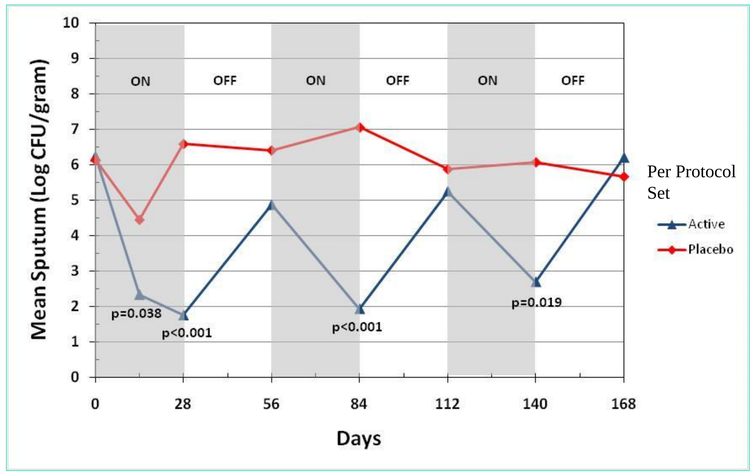
Activaero Akita Jet System using the PARI LC Sprint nebulizer

PARI LC Sprint® nebulizer and PARI TurboBoy-S® compressor

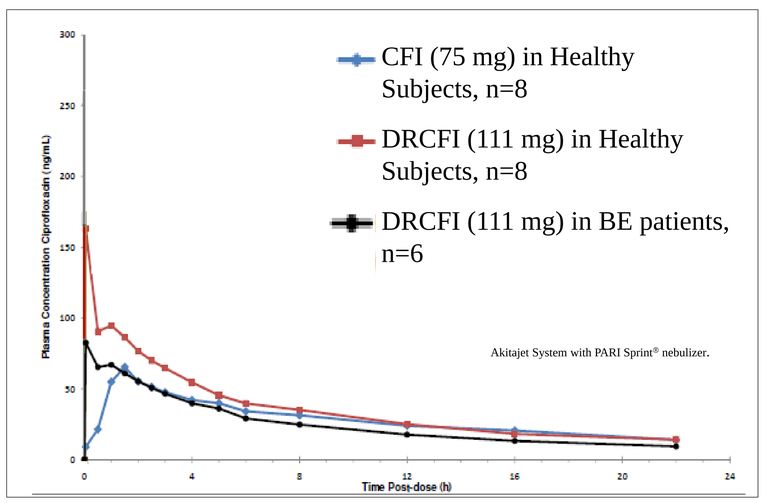
CFI Liposome Vesicle Size Distribution is Stable at 5°C



ORBIT-2: Significant Antimicrobial Effect over 6 Months



Pharmacokinetic profile of DRCFI vs CFI in Healthy Subjects and Bronchiectasis

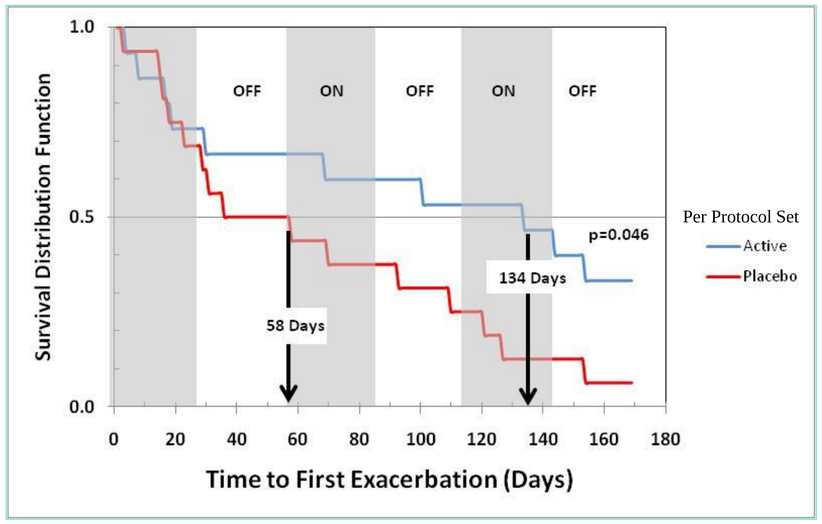


CFI Liposomes are Robust to Nebulization

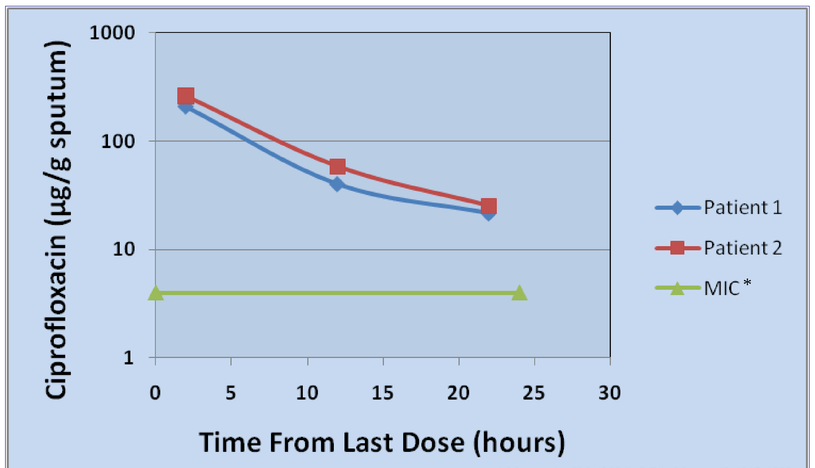
Batch Number	Control		Nebulizer[1]			Collected Aerosol			Mass Balance
	Encapsulation (%)	Mean Size (nm)	Recovery (%)	Encapsulation (%)	Mean Size (nm)	Emitted Dose (%)	Encapsulation (%)	Mean Size (nm)	%
7155A	99.6 ± 0.1	89.4	41.8 ± 1.6	99.4 ± 0.2	92.7	53.3 ± 1.1	96.0 ± 0.1	89.9	95.1
7156A	99.6 ± 0.1	90.6	39.8 ± 2.3	99.5 ± 0.0	90.7	56.0 ± 0.6	96.4 ± 0.2	91.7	95.8
7157A	99.5 ± 0.1	86.2	39.5 ± 0.2	99.4 ± 0.1	85.6	54.6 ± 1.9	97.0 ± 0.4	85.7	94.1
7158A	99.6 ± 0.0	90.4	44.0 ± 0.2	99.6 ± 0.0	96.1	51.9 ± 0.9	96.9 ± 0.9	93.0	95.9
7159A	97.0 ± 2.5	74.7	34.1 ± 2.3	98.5 ± 1.1	83.6	60.5 ± 1.3	96.1 ± 2.3	83.8	94.6
7160A	99.6 ± 0.1	89.3	42.0 ± 2.5	99.4 ± 0.2	88.2	53.9 ± 1.3	96.5 ± 0.9	91.3	95.9
8096A	99.6 ± 0.0	83.8	42.0 ± 0.3	99.6 ± 0.0	86.2	52.3 ± 1.1	97.1 ± 0.4	88.8	94.3
8097A	99.5 ± 0.1	86.8	40.3 ± 4.6	99.6 ± 0.0	88.0	52.3 ± 1.9	97.0 ± 0.1	NT	92.6
8098A	98.8 ± 1.0	91.5	40.6 ± 1.6	99.6 ± 0.1	90.5	55.4 ± 1.7	97.2 ± 0.1	NT	96.0
Mean	99.2 ± 0.9	87.0 ± 5.2	40.5 ± 2.8	99.4 ± 0.4	89.1 ± 3.9	54.5 ± 2.7	96.7 ± 0.5	89.2 ± 3.3	94.9 ± 1.1

[1] 3 mL volume nebulized (n=3 per lot) after 24 months at 5°C (± Std. Dev) NT = Not Tested

ORBIT-2: Once Daily DRCFI Improves Time to First Exacerbation



Ciprofloxacin Sputum Levels Exceed MIC and Support QD Dosing



* Moskowitz SM, (2004), J Clin Microb 42:1915-1922

Acknowledgements

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SUMMARY

- CFI (ARD-3100) and DRCFI (ARD-3150) are safe and well-tolerated in healthy subjects and patients with bronchiectasis (BE).
- PK profiles of CFI and DRCFI in healthy subjects and BE patients demonstrate lung absorption-limited plasma half life (t½) of ~10 hr, compatible with once-a-day dosing.
- DRCFI reduced *P. aeruginosa* by 4.4 log10 CFU units versus a mean increase of 0.1 log10 units in the placebo group ($p<0.001$) at Day 28.
- The Kaplan Meier analysis demonstrated a statistically significant ($p<0.046$, log rank test) increase in the median time to first pulmonary exacerbation from 58 days (Placebo) to 134 days (DRCFI).
- DRCFI had a superior pulmonary safety profile reflected in the number and severity of pulmonary adverse events.
- The sustained release profile of inhaled DRCFI and its effect in reducing PA sputum density and exacerbations in BE warrant further clinical development.

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