Pharmacokinetic-Pharmacodynamics of Delafloxacin Against *Haemophilus Influenzae* Using Data from a One-Compartment *In Vitro* Infection Model

B.D. VanScoy[1], H. Conde[1], S.P. McCurdy[2], K. Keedy[2], P.G. Ambrose[1], S.M. Bhavnani[1]
[1]Institute for Clinical Pharmacodynamics, Inc., Schenectady, NY, USA;
[2]Melinta Therapeutics, Inc., Morristown, NJ, USA

INSTITUTE for CLINICAL PHARMACODYNAMICS

Brian D. VanScoy, B.S.
Institute for Clinical Pharmacodynamics, Inc.
242 Broadway
Schenectady, NY 12305
Telephone: (518) 631-8100
Fax: (518) 631-8199
Email: bvanscoy@ICPD.com

INTRODUCTION

- Delafloxacin is an anionic fluoroquinolone with *in vitro* activity against pathogens associated with various infection types, including acute bacterial skin and skin structure (for which it was approved by the US FDA) and community-acquired bacterial pneumonia (CABP) [1].
- *Haemophilus influenzae* represents one of the leading causes of CABP [2].
- The goal of the studies described herein was to use a one-compartment *in vitro* infection model to characterize the pharmacokinetic-pharmacodynamics (PK-PD) of delafloxacin against *H. influenzae*.
  - Since the PK-PD index associated with fluoroquinolone efficacy has been shown to be AUC:MIC ratio [3], the magnitude of this index associated with efficacy for a panel of five clinical *H. influenzae* isolates was determined.

METHODS

Antimicrobial Agent and Challenge Isolates

- Delafloxacin was supplied by Melinta Therapeutics (New Haven, CT).
- *H. influenzae* clinical isolates were provided by JMI Laboratories (North Liberty, IA).

In Vitro Susceptibility Testing

- Susceptibility studies were completed in triplicate over a two day period, following Clinical Laboratory Standards Institute (CLSI) guidelines [4].

One-Compartment *In Vitro* Infection Model Dose-Ranging Studies

- A suspension of each challenge isolate was prepared at a concentration of 1.0×10^6 colony forming units (CFU)/mL.
- Bacteria in the central infection compartment were exposed to delafloxacin free-drug plasma exposures associated with doses ranging from 0.09 to 1500 mg administered every 12 hours (q12h).
- Samples were collected from the central infection compartment for CFU determination and drug concentration analysis at pre-determined time points throughout the duration of the study.

Pharmacokinetic-Pharmacodynamic Analysis

- Hill-type models were used to evaluate the relationship between change in $\log_{10}$ CFU/mL from baseline at 24 hours and delafloxacin free-drug plasma AUC:MIC ratio based on data from each isolate and all isolates pooled.

RESULTS

In Vitro Susceptibility Testing

- The delafloxacin microbroth MIC values ranged from 0.001 to 1 mg/L.

One-Compartment *In Vitro* Infection Model Dose-Ranging Studies

- The targeted free-drug plasma concentration-time profiles for delafloxacin were well simulated in the one-compartment model for all dosing regimens, as evidenced by the agreement between the targeted and observed concentrations shown in **Figure 1** and **Figure 2**.
- The relationship between change in $\log_{10}$ CFU/mL from baseline at 24 hours and the delafloxacin free-drug plasma AUC:MIC ratio, examined based on pooled data, is shown in **Figure 3**.
  - As evidenced by the coefficient of determination (r^2) value of 0.812 and the dispersion of data along the fitted line, free-drug plasma AUC:MIC ratio described the efficacy of delafloxacin well across the clinical *H. influenzae* isolates.
- Hill models describing the relationship for individual isolates also described these data well (r^2 values of 0.823 to 0.989).
- The median delafloxacin free-drug plasma AUC:MIC ratio associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU/mL reductions from baseline at 24 hours was 23.5, 28.7, and 36.0, respectively (**Table 1**).

Figure 1. Relationship between targeted and observed delafloxacin concentrations simulated in the one-compartment *in vitro* infection model

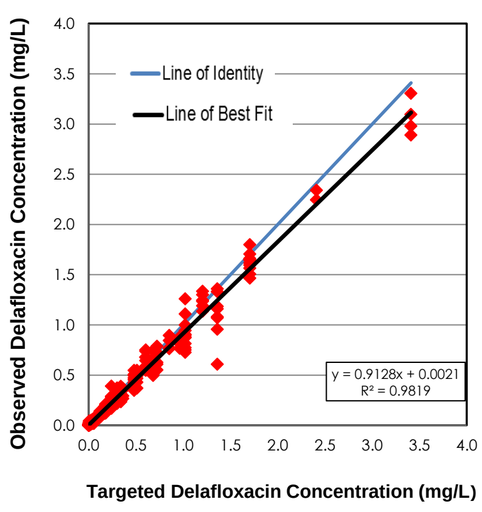

Figure 2. Targeted delafloxacin plasma concentration-time profile for a delafloxacin 300 mg q12h dosing regimen, with observed concentrations overlaid

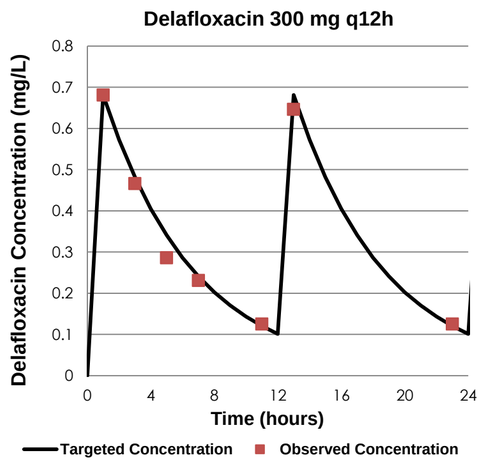

Figure 3. Relationship between change in $\log_{10}$ CFU/mL from baseline at 24 hours and delafloxacin free-drug plasma AUC:MIC ratio based on pooled data for five *H. influenzae* isolates studied using the one-compartment *in vitro* infection model

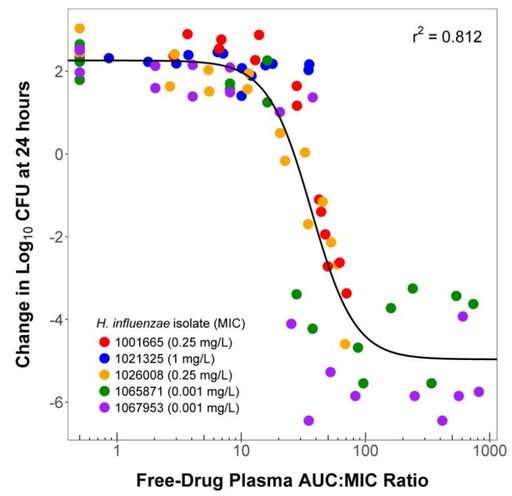

Table 1. Delafloxacin free-drug plasma AUC:MIC ratio targets associated with various levels of bacterial reduction from baseline for five *H. influenzae* isolates

H. influenzae isolate	Delafloxacin free-drug plasma AUC:MIC ratio targets		
	Net bacterial stasis	1-$\log_{10}$ CFU/mL reduction	2-$\log_{10}$ CFU/mL reduction
1065871	21.1	22.7	24.4
1067953	17.4	21.7	26.6
1026008	26.0	34.7	45.5
1001665	35.5	40.7	47.6
1021325[a]	N/A	N/A	N/A
Pooled with isolate 1021325[b]	26.6	33.8	42.3
Pooled without isolate 1021325[c]	23.6	30.4	38.6
Median	23.5	28.7	36.0

a. No reduction in bacterial burden from baseline at 24 hours was observed for *H. influenzae* 1021325 across the delafloxacin dosing regimens studied (37.5 to 1500 mg q12h).
b. Determined using a Hill model based on pooled data for the five *H. influenzae* isolates.
c. Determined using a Hill model based on pooled data for the four *H. influenzae* isolates, excluding isolate 1021325.

CONCLUSIONS

- Studies using a one-compartment *in vitro* infection model to characterize the magnitude of delafloxacin free-drug plasma AUC:MIC ratio associated with efficacy for *H. influenzae* were successfully completed.
  - The median free-drug AUC:MIC ratios associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU/mL reductions from baseline at 24 hours were 23.5, 28.7, and 36.0, respectively.
- These data provide insight about the PK-PD of delafloxacin against *H. influenzae* and are useful to evaluate delafloxacin dose selection for patients with CABP.

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