Pharmacokinetic-Pharmacodynamic Target Attainment Analyses for Delafloxacin to Provide Dose Selection Support for the Treatment of Patients with Community-Acquired Bacterial Pneumonia

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ABSTRACT

Background: Delafloxacin is an investigational IV and PO quinolone with activity against pathogens commonly associated with community-acquired bacterial pneumonia (CABP), including *Streptococcus pneumoniae* (SP) and *Staphylococcus aureus* (SA), including methicillin-resistant isolates. To provide support for a delafloxacin IV to PO dosing regimen to treat patients with CABP, PK-PD target attainment analyses were undertaken.

Methods: Using parameter estimates from a population PK model [3-compartments; mixed linear plus saturable elimination; 2 parallel first-order absorption processes; creatinine clearance (CLcr) was a predictor of clearance], free-drug plasma concentration-time profiles were generated for 5,000 simulated patients with varying CLcr following delafloxacin 300 mg IV q12h for 3 days followed by 450 mg PO q12h for 2 days. $AUC_{0\text{-}24}$ on Days 1 and 4 were calculated. Percent probabilities of PK-PD target attainment by MIC and overall (i.e., weighted over the MIC distributions for SP and SA isolates from USA and Europe) were determined using median free-drug plasma AUC:MIC ratio targets associated with 1- and 2-$\log_{10}$ CFU reductions from baseline from a neutropenic lung infection model for SP (3.36 and 24.5, respectively) and SA (7.92 and 36.2, respectively). The results were stratified by renal function group [normal (CLcr ≥90 mL/min/1.73 m^2) and mild (CLcr 60 to 89 mL/min/1.73 m^2) or moderate (CLcr 30 to 59 mL/min/1.73 m^2) renal impairment].

Results: Percent probabilities of attaining free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline by MIC on Day 1 by renal group for SP (Figure 1A) and SA (Figure 1B) were similar to those on Day 4. Percent probabilities of PK-PD target attainment on either day across renal groups were ≥99.5% for SP at a MIC value of 1 mg/L and ≥96.3% for SA at a MIC value of 0.5 mg/L. Overall percent probabilities of PK-PD target attainment were ≥93.3%. For free-drug plasma AUC:MIC ratio targets associated with a 2-$\log_{10}$ CFU reduction from baseline, percent probabilities of PK-PD target attainment at a MIC value of 0.12 mg/L on either Days 1 or 4 were ≥99.8 and ≥93.7% for SP and SA, respectively.

Conclusions: These data provide support for delafloxacin 300 mg IV q12h for 3 days followed by 450 mg PO q12h for 2 days to treat patients with CABP who have normal renal function or mild or moderate renal impairment.

INTRODUCTION

- Delafloxacin is an intravenously (IV) and orally (PO) administered investigational antibiotic of the quinolone class with *in vitro* activity against pathogens commonly associated with community-acquired bacterial pneumonia (CABP), including *Streptococcus pneumoniae*, *Haemophilus influenzae, Moraxella catarrhalis*, methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) and atypical organisms [1].
- Given the spectrum of *in vitro* activity against these pathogens, IV and PO formulations of delafloxacin are being developed for the treatment of patients with CABP.
- Using a previously-developed population PK model for delafloxacin [2], non-clinical PK-PD targets for efficacy [3], *in vitro* surveillance data [4, 5], and Monte Carlo simulation, PK-PD target attainment analyses were conducted to provide delafloxacin dose selection support for the treatment of patients with CABP.

OBJECTIVE

- The objective of these analyses was to assess the percent probabilities of PK-PD target attainment of a delafloxacin dosing regimen of 300 mg IV q12h for 3 days, followed by 450 mg PO q12h for 2 days for the treatment of patients with CABP with normal renal function or mild or moderate renal impairment.

METHODS

Simulated Patient Population

- The generation of delafloxacin exposure in simulated patients required the use of the previously-developed population PK model [2] described below.
  - The population PK model was developed using pooled data from four Phase 1 studies and consisted of a three-compartment model with mixed linear and non-linear Michaelis-Menten elimination and a complex absorption model. The absorption model involved parallel immediate and delayed absorption processes.
  - The following statistically significant covariate relationships were identified:
    - The linear portion of clearance (CL_{LN}) decreases with decreasing baseline CLcr;
    - The volume of the central compartment (Vc) increases with increasing WTKG; and
    - Immediate absorption rate (Ka_1) was faster under fasted conditions compared to Ka_1 after a high-fat/high calorie meal.
- A dataset of simulated patients (n=5,000) with varying renal function was generated in SAS® Version 9.4.
  - A bootstrapping method was used to replicate the distribution of CLcr and WTKG reported in a previously-described population of patients with CABP [6].
  - Since the population PK analysis suggested that delafloxacin bioavailability was not impacted by food [2], separate simulations were not conducted to compare PK-PD target attainment under fed and fasted conditions. Instead, simulated patients were randomly assigned to receive delafloxacin under fed or fasted conditions with equal probability in order to mimic the likely extremes of the clinical scenarios of a Phase 3 study.
  - PK parameter estimates for the above-described 5,000 simulated patients were generated using population PK model for delafloxacin [2].
- Total-drug plasma concentration-time profiles were generated for each simulated patient after administration of delafloxacin 300 mg IV q12h for 3 days followed by 450 mg PO q12h for 2 days.
- Day 1 and 4 total-drug plasma area under the concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) were calculated using the linear trapezoidal rule; free-drug plasma $AUC_{0\text{-}24}$ was calculated assuming a free fraction of 0.16 [7].
- Day 1 free-drug plasma $AUC_{0\text{-}24}$ values were divided by MIC values ranging from 0.004 to 4 mg/L to calculate the ratio of free-drug plasma $AUC_{0\text{-}24}$ to MIC (AUC:MIC ratio).

Non-Clinical PK-PD Targets for Efficacy

- Free-drug plasma AUC:MC ratio targets for efficacy for *S. pneumoniae* and *S. aureus* evaluated, as shown in **Table 1**, were based on data from neutropenic murine-lung infection models [3]. Emphasis was placed on the assessment of the median free-drug plasma targets associated with a 1-$\log_{10}$ CFU reduction from baseline.

Table 1. Free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* and *S. aureus* efficacy

Pathogen	Bacterial reduction endpoint ($\log_{10}$ CFU reduction from baseline)	Median free-drug plasma AUC:MIC ratio
S. pneumoniae	1	3.36
	2	24.5
S. aureus	1	7.92
	2	36.2

METHODS

Delafloxacin *In Vitro* Activity

- The MIC distributions for delafloxacin against *S. pneumoniae* and *S. aureus* considered for calculation of overall percent probability of PK-PD target attainment were based on 450 and 1,350 isolates, respectively, collected from North America and the European Union combined [4, 5].

Evaluation of PK-PD Target Attainment

- Percent probabilities of PK-PD target attainment by MIC and weighted over the above-described MIC distributions based on free-drug plasma exposures for delafloxacin were determined for each of the free-drug plasma AUC:MIC ratio targets described in **Table 1**.

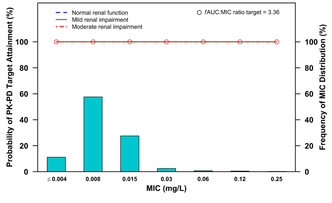
RESULTS

- Summary statistics of CLcr for the population of 5,000 simulated patients are presented in **Table 2.**

Table 2. Summary statistics of CLcr for the simulated patient population

Renal function group	CLcr (mL/min/1.73 m^2)			
	Median	Min	Max	N (%)
Normal renal function	114	90.3	188	1,302 (26.0)
Mild impairment	71.2	60.1	89.7	2,025 (40.5)
Moderate impairment	43.9	30.2	59.0	1,673 (33.5)
Total	69.5	30.2	188	5,000 (100)

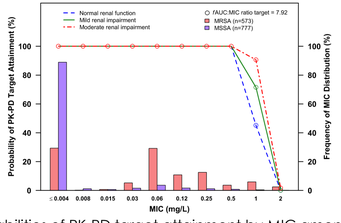
Figure 1. Percent probabilities of PK-PD target attainment by MIC on Day 1 based on the evaluation of the free-drug plasma AUC:MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* among simulated patients stratified by renal function group, overlaid on the MIC distribution for *S. pneumoniae*



- As shown in **Figure 1**, percent probabilities of PK-PD target attainment among simulated patients were 100% across the *S. pneumoniae* MIC distribution. Similar results were evident for assessments made on Day 4.
- Percent probabilities of attaining the free-drug plasma AUC:MIC ratio target associated with a 2-$\log_{10}$ CFU reduction from baseline at the MIC value of 0.12 mg/L (i.e., covering 99.8% of *S. pneumoniae* isolates) were 100 and ≥ 99.8% on Days 1 and 4, respectively.

RESULTS

Figure 2. Percent probabilities of PK-PD target attainment by MIC on Day 1 based on the evaluation of the free-drug plasma AUC:MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus* among simulated patients stratified by renal function group, overlaid upon the MIC distributions for MRSA and MSSA



- Percent probabilities of PK-PD target attainment by MIC among simulated patients stratified by renal group overlaid on the MIC distributions for MRSA and MSSA on Day 4 were similar to the assessments for Day 1 shown in **Figure 2**.
- Percent probabilities of attaining the free-drug plasma AUC:MIC ratio target associated with a 2-$\log_{10}$ CFU reduction from baseline at MIC value of 0.12 µg/mL (i.e., covering 75.4% and 97.6% of MRSA and MSSA isolates, respectively) were ≥99.8 and ≥93.7% on Days 1 and 4, respectively.

Table 3. Overall probabilities of PK-PD target attainment

Pathogen	Renal Function Group	Overall probabilities of PK-PD target attainment			
		1-$\log_{10}$		2-$\log_{10}$	
		Day 1	Day 4	Day 1	Day 4
S. pneumoniae	Normal renal function	100	100	100	99.9
	Mild impairment	100	100	100	100
	Moderate impairment	100	100	100	100
MSSA	Normal renal function	99.7	99.6	97.8	97.7
	Mild impairment	99.8	99.7	98.1	97.9
	Moderate impairment	99.8	99.8	98.4	98.2
MRSA	Normal renal function	94.3	93.3	78.0	76.9
	Mild impairment	95.9	94.8	81.1	79.6
	Moderate impairment	97.0	96.3	84.9	82.9

- As shown in **Table 3**, overall percent probabilities of PK-PD target attainment based on the evaluation of the free-drug plasma AUC:MIC ratio target associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* and *S. aureus* were ≥93.3%.

CONCLUSIONS

- These data provide dose support for administration of delafloxacin 300 mg IV q12h for 3 days followed by 450 mg PO q12h for 2 days in an ongoing clinical trial to treat patients with CABP who have normal renal function or mild or moderate renal impairment.
- The implications of these finding will need to be evaluated in the context of exposures in humans and murine PK-PD targets for efficacy.

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