Pharmacokinetic-Pharmacodynamic Target Attainment Analyses Supporting Delafloxacin Phase 3 Dose Regimen Decisions

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ABSTRACT

Background: DFX is a broad spectrum quinolone with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) being developed for the treatment of acute bacterial skin and skin-structure infections (ABSSSI).
Methods: Monte Carlo simulation (n=1,000) using clinical PK and non-clinical PK-PD data were utilized to determine PK-PD target attainment (TA) probabilities by MIC for DFX 200-450 mg IV q12h. The parameter mean vector and the variance-covariance matrix, from a previous population PK model, was used to simulate PK profiles and predict $AUC_{0\text{-}24}$. This model, which was developed using data from 258 subjects in 7 Phase 1 and 1 Phase 2 studies, fit the data well as evidenced by an r^2 of 0.944 for observed vs individual fitted concentrations and without significant biases. Resultant free-drug $AUC_{0\text{-}24}$ values (adjusted using a free fraction estimate of 16.3%) were divided by fixed MIC values (0.0004-8.0 mg/L). Using free-drug $AUC_{0\text{-}24}$:MIC ratio targets associated with net bacterial stasis and 1-$\log_{10}$ CFU reduction from baseline in neutropenic murine-thigh infection models evaluating DFX against *S. aureus* of 9.3 and 14.3, respectively (ICAAC 2009, A1-1941), % probabilities of PK-PD TA by MIC, and overall across an MIC distribution for MRSA, were computed for each dosing regimen.
Results: PK-PD TA % probabilities by MIC and overall for DFX regimens evaluated are shown below.
Conclusions: Given the current MIC distribution for MRSA, excellent overall PK-PD TA rates were achieved for the regimens evaluated; 300 and 450 mg IV q12h are predicted to achieve generally high PK-PD TA rates for MIC ≤ 0.5 mg/L. These results will be utilized to support Phase 3 dose selection decisions for patients with ABSSSI.

DFX dosing regimen	Percent probability of PK-PD target attainment by MIC (mg/L) based on attaining free-drug $AUC_{0\text{-}24}$:MIC ratio targets for net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline[1]					
	0.06	0.12	0.25	0.5	1.0	Overall[2]
200 mg q12h	100/100	100/99	98/79	47/0	0/0	91/85
300 mg q12h	100/100	100/100	100/99	95/59	18/0	94/92
450 mg q12h	100/100	100/100	100/100	100/98	88/27	96/94

1. Based on free-drug $AUC_{0\text{-}24}$:MIC ratio targets of 9.3 and 14.3 for net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus*, respectively.
2. Overall % probability of PK-PD target attainment across an MIC distribution for MRSA (the minimum, maximum, MIC_{50} and MIC_{90} values for which were ≤0.004, 8, 0.12 and 0.5 mg/L, respectively).

INTRODUCTION

- Delafloxacin is an investigational antibiotic of the fluoroquinolone class distinguished by excellent antibacterial activity against gram-positive organisms including both methicillin-susceptible and –resistant *Staphylococcus aureus* (MSSA and MRSA) and is currently being developed for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI).
- Knowledge gained about relationships between the pharmacokinetics (PK) and pharmacodynamics (PD) for antibacterial agents is critical to support dose selection in clinical drug development. Pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses, which are conducted using Monte Carlo simulation, and population PK and non-clinical PK-PD data, are useful to support dose selection decisions.
- Using a previously-developed population PK model for IV delafloxacin [1] and non-clinical PK-PD data [2], PK-PD target attainment analyses were conducted for delafloxacin to support dose selection for clinical trials in patients with ABSSSI.

METHODS

Simulated Subjects and Exposure Estimates
- Monte Carlo simulation was performed based upon the population PK model for IV data only.
- Using the mean parameter vector and the variance-covariance matrix from the population PK model, PK parameter estimates were simulated for 1,000 hypothetical subjects.
- Plasma PK profiles for the 1,000 simulated subjects were generated and total-drug area under the concentration-time curve from zero to 24 hrs ($AUC_{0\text{-}24}$) on Day 1 was calculated by integrating the PK profile in very small time increments for each subject for each of the delafloxacin dosing regimens described below.

Dosing Regimens Evaluated
- 200 mg infused over 1 hour twice daily (q12h),
- 300 mg infused over 1 hour q12h, and
- 450 mg infused over 1 hour q12h.

Protein Binding Assumption
- Free-drug $AUC_{0\text{-}24}$ estimates on Day 1 were calculated using a fixed protein binding estimate of 0.163.

Basis for PK-PD Target
- PK-PD targets were based on data from a neutropenic murine-thigh infection model [2]. A brief summary of these findings is described below.
  - Mice were infected with 1 of 5 *S. aureus* isolates, *S. aureus* 2926 (USA100; MRSA), 11540 (USA300; MRSA), MRSA 11512, MSSA ATCC 29213, and MSSA Smith. The MIC values of delafloxacin against these organisms are 0.016, 0.8, 0.5, 0.006 and 0.004 µg/mL, respectively.
  - The ratio of $AUC_{0\text{-}24}$ to minimum inhibitory concentration ($AUC_{0\text{-}24}$:MIC) was identified to be the PK-PD measure best predictive of delafloxacin efficacy.
  - Median free-drug $AUC_{0\text{-}24}$:MIC ratios of 9.3 and 14.3 were associated with net bacterial stasis and 1-$\log_{10}$ colony forming units (CFU) decrease in these studies, respectively.

MIC Distribution
- The MIC distribution was determined using MRSA skin and wound infection isolates from 2007-2008, collected from the Eurofins Surveillance Network. Isolates were gathered from the United States, European Union and the Asia/Pacific region

RESULTS

- Comparison of the population PK parameter estimates and interindividual variability for these estimates and the median (CV%) of the PK parameter estimates for the 1,000 simulated subjects indicated that the simulation replicated the expected distributions appropriately (**Table 1**).
- The broth microdiulation MIC distribution for MRSA skin and wound infection isolates used for the simulation (n=994), the minimum, maximum, MIC_{50} and MIC_{90} values for which were 0.004, 8, 0.12, 0.5 mg, are shown in **Table 2**.
- A subset of results for the percent probability of PK-PD target attainment by MIC and the overall percent probability of target attainment across the MIC distribution for MRSA is shown in **Table 3**.
- Graphical displays showing probabilities of PK-PD target attainment by MIC overlaid on the MIC distribution for MRSA based on each of the two PK-PD targets evaluated, are shown for each delafloxacin dosing regimen in **Figure 1**.

RESULTS

Table 1. Comparison of PK parameters for simulated patients to population PK parameters

	Population mean (interindividual variability)	Simulated data median (CV%)
Vc (L)	26.6 (15.7)	26.8 (15.5)
CLd (L/hr)	6.76 (63.1)	7.01 (65.0)
Vp (L)	33.1 (48.2)	33.4 (50.0)
CLi (L/hr)	29.4 (70.1)	29.0 (75.7)
Km (µg/mL)	0.506 (55.1)	0.508 (60.9)
CL1 (L/hr)	6.78 (24.3)	6.79 (25.5)

Vc is the apparent volume of distribution of the central compartment; CLd is the distributional clearance; Vp is the apparent volume of distribution of the peripheral compartments; Cli is intrinsic clearance; Km is Michaelis-Menten constant.

Table 2. Broth microdilution MIC distribution for delafloxacin against MRSA based on surveillance data

MIC (mg/L)	n	%	Cumulative %
≤ 0.004	274	27.6	27.6
0.008	20	2.0	29.6
0.015	11	1.1	30.7
0.03	18	1.8	32.5
0.06	148	14.9	47.4
0.12	232	23.3	70.7
0.25	184	18.5	89.2
0.5	45	4.5	93.8
1	26	2.6	96.4
2	22	2.2	98.6
4	11	1.1	99.7
8	3	0.3	100.0
Total:	**994**		

Table 3. Percent probability of PK-PD target attainment by MIC based on attaining free-drug $AUC_{0\text{-}24}$:MIC targets for net bacterial stasis and 1-$\log_{10}$ CFU reduction from baseline

Delafloxacin dosing regimen	Percent probability of PK-PD target attainment by MIC (mg/L) based on attaining free-drug AUC:$MIC_{0\text{-}24}$ ratio targets for net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline[1]					
	0.06	0.12	0.25	0.5	1.0	Overall[2]
200 mg q12h	100/100	100/99	98/79	47/0	0/0	91/85
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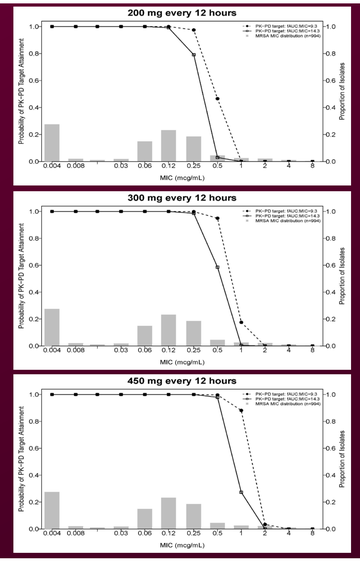
1. Based on free-drug AUC:$MIC_{0\text{-}24}$ ratio targets of 9.3 and 14.3 for net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus*, respectively.
2. Overall % probability of PK-PD target attainment across an MIC distribution for MRSA (the minimum, maximum, MIC_{50} and MIC_{90} values for which were ≤0.004, 8, 0.12 and 0.5 mg/L, respectively).

RESULTS

Figure 1. Graphical displays of probabilities of PK-PD target attainment by MIC overlaid on the MRSA MIC distribution for each delafloxacin dosing regimen



- For the 300 mg q12h dosing regimen, percent probabilities of PK-PD target attainment with net bacterial stasis approached 100% for MIC values up to and including 0.5 mg/L (the MIC_{90} for the MRSA distribution).
- The percent probability of PK-PD target attainment approached 90% for the 450 mg q12h dosing regimen for the net bacterial stasis target at a MIC of 1 mg/L.

Conclusions

- Given the current MIC distribution for MRSA, excellent overall percent probabilities of PK-PD target attainment were achieved for the delafloxacin dosing regimens evaluated; percent probabilities of target attainment for delafloxacin 300 and 450 mg IV q12h were generally high for MIC ≤ 0.5 mg/L.
- These results will be utilized to support Phase 3 dose selection decisions for patients with ABSSSI.

1. Rubino CM, et al. Delafloxacin population pharmacokinetics and covariate exploration. [Abstract A1-682]. Interscience Conference on Antimicrobial Agents and Chemotherapy. Boston, MA. Sept. 12-15, 2010.
2. Burak E, et al. Pharmacokinetics and phamacodynamics of delafloxacin in S. aureus murine thigh infection models. [Abstract A1-1941]. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, CA. Sept. 12-15, 2009.

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