Population Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Target Attainment Analyses for Delafloxacin to Support Dose Selection for the Treatment of Patients with Acute Bacterial Skin and Skin Structure Infections

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INTRODUCTION

- Delafloxacin is a novel fluoroquinolone with activity against pathogens associated with acute bacterial skin and skin structure infection (ABSSSI), including methicillin-susceptible and -resistant *Staphylococcus aureus*. Delafloxacin was recently approved by the United States Food and Drug Administration for the treatment of patients with ABSSSI.
- As part of the drug development program, two Phase 3 clinical trials were completed in patients with ABSSSI [1, 2]. Pharmacokinetic (PK) data from these two clinical trials provided the opportunity to refine an existing population PK and conduct pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses to provide support for a delafloxacin intravenous (IV) to oral (PO) dosing regimen to treat patients with ABSSSI, including those with renal impairment.

OBJECTIVES

- The objectives of these analyses were the following:
  - To develop a population PK model for IV delafloxacin using pooled data from healthy subjects and patients enrolled in Phase 1, 2, and 3 studies.
  - To use the above-described population PK model, non-clinical PK-PD targets for efficacy, and Monte Carlo simulation in order to carry out PK-PD target attainment analyses to evaluate delafloxacin 300 mg IV q12h on Days 1-3 followed by 450 mg PO q12h on Day 4 and dosing regimens for renal impairment for the treatment of patients with ABSSSI.

METHODS

Population Pharmacokinetic Analyses

- Data to be used for the analyses were obtained from four Phase 1 studies, one Phase 2 study, and two Phase 3 studies [1,2].
  - The two Phase 3 studies consisted of patients with ABSSSI. In the first study, delafloxacin 300 mg IV q12h was administered. In the other study, six doses of delafloxacin 300 mg IV q12h were administered followed by a mandatory switch to delafloxacin 450 mg PO q12h for the remaining doses. Patients in the second study assigned to the delafloxacin arm and who had creatinine clearance (CLcr) of 15 to 29 mL/min at screening received delafloxacin 200 mg IV q12h for all doses.
- Candidate population PK models were fit to the pooled PK data using NONMEM® software Version 7.2.
- Multi-compartment disposition model structures with linear and mixed linear and nonlinear elimination processes were fit to the data.
- After an appropriate structural model was identified, population PK covariate model development was undertaken using forward selection followed by a backward elimination procedure.
  - Covariate exploration involved graphical examination of plots of PK parameters versus demographic characteristics, followed by development of the covariate model using NONMEM.
  - The appropriateness of the structural and variance models was assessed throughout the process and refined as necessary.
  - Monte Carlo simulations were conducted to facilitate the interpretation of any covariate relationships identified during model development.

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

- To assess PK-PD target attainment among simulated patients with varying renal function, simulated patient populations varying by ranges of CLcr were generated as shown in **Table 1**. Using a resampling method, simulated patients resembling the clinical trial were also generated. Simulations were performed using SAS® Version 9.4.

METHODS

- Free-drug AUC values were generated for each simulated patient using Monte Carlo simulation from the final population PK model. The free fraction was assumed to be 16%. Bioavailability after oral administration was derived from a previous population PK model for delafloxacin [3].
- Simulated patients received delafloxacin dosing regimens according to CLcr as described in **Table 1**.
- Percent probabilities of PK-PD target attainment by MIC and overall (i.e., weighted over *S. aureus* MIC distributions) were determined using median free-drug AUC:MIC ratio targets associated with net bacterial stasis and a 1-$\log_{10}$ CFU reduction from baseline from a neutropenic murine-thigh infection model (9.3 and 14.3, respectively) [4].

Table 1. Summary of delafloxacin dosing regimens by renal function group as defined by CLcr ranges

Renal function group (CLcr range in mL/min/1.73 m^2)	Delafloxacin dosing regimen
Normal renal function (≤90 to <200 mL/min/1.73 m^2)	300 mg IV q12h on Days 1-3 followed by 450 mg PO q12h on Day 4
Mild renal impairment (≤60 to <90 mL/min/1.7 $3m^2$)	
Moderate renal impairment (≤30 to <60 mL/min/1.73 m^2)	
Severe renal impairment (15≤30 mL/min/1.73 m^2)	200 mg IV q12h on Days 1-3 followed by 450 mg PO q12h on Day 4
ESRD without dialysis (≤5 to <15 mL/min/1.73 m^2)	
ESRD with dialysis (≤5 to <15 mL/min/1.73 m^2)	

ERSD = End stage renal disease

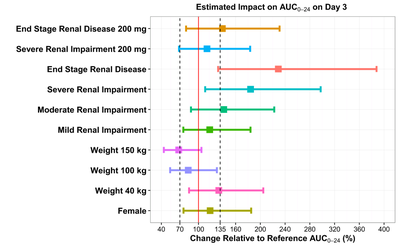
RESULTS

Population Pharmacokinetic Analyses

- The most robust fit to the data was obtained using a three-compartment model with mixed linear and nonlinear clearance.
- Population PK covariate model development analyses resulted in the identification of the following statistically significant covariate relationships:
  - The linear portion of clearance (CLLN) increases with increasing baseline CLcr and body weight with CLLN approximately 20% lower in females relative to males;
  - The volume of the central compartment and the volume of peripheral compartment both increases with increasing body weight; and
  - The renal clearance (CLR) increases with increasing CLcr.
- The final population PK model fit the observed concentrations with a high degree of accuracy and precision.
- Of the above-described covariate relationships, only the relationship between CLcr and CL_{LN} was clinically relevant (**Figure 1**).

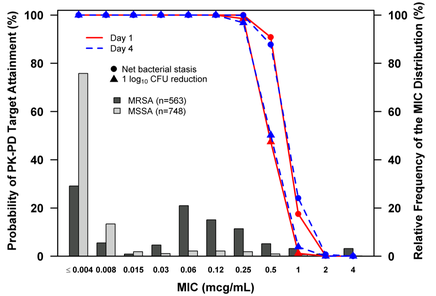
RESULTS

Figure 1. Forest plot of covariate effects on delafloxacin plasma $AUC_{0\text{-}24}$ on Day 3 after delafloxacin IV administration



Note: The demographic characteristics of simulated reference patients (n=500) were as follows: male patients with CLcr of 120 mL/min/1.73 m^2 and weight of 70 kg. The delafloxacin geometric mean plasma $AUC_{0\text{-}24}$ on Day 3 for the simulated reference patients is represented by the red solid vertical line. The black dashed vertical lines represent 70 and 135% of the reference $AUC_{0\text{-}24}$ for simulated reference patients. The solid square and error bars represent the median and 90% confidence interval for the fold change of delafloxacin plasma $AUC_{0\text{-}24}$ on Day 3 relative to the reference $AUC_{0\text{-}24}$ for simulated patients (n= 500).

Figure 2. Percent probabilities of PK-PD target attainment by MIC among simulated patients with ABSSSI after administration of delafloxacin dosing regimens



Pharmacokinetic-Pharmacodynamic Target Attainment Analyses

- As shown in **Table 2**, percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 were similar across renal groups.
  - At the MIC_{90} of 0.25 µg/mL for *S. aureus*, percent probabilities of attaining a free-drug AUC:MIC ratio associated with net bacterial stasis on either Days 1 or 4 were ≥ 99.5%.
  - Overall percent probabilities ranged from 91.9 to 99.8%.
- As shown in **Figure 1**, percent probabilities of attaining a free-drug AUC:MIC ratio associated with net bacterial stasis were 100 and 99.9% on Days 1 and 4, respectively, at the MIC_{90} value among simulated patients resembling the clinical trial population.

Table 2. Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 for delafloxacin 300 mg IV q12h on Days 1 to 3 followed by 450 mg PO q12h on Day 4 based on the free-drug plasma AUC:MIC ratio targets for *S. aureus* efficacy among simulated patients

Endpoints for free-drug plasma AUC:MIC ratio targets	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 among simulated patients													
		Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment[b]		ESRD without dialysis[b]		ERSD with dialysis[b]		All patients	
		Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
Net bacterial stasis	0.25	99.9	99.5	100	100	100	100	100	100	100	100	99.8	100	100	99.9
	0.5	81.6	77.8	95.1	92.5	98.4	97.1	89.2	98.3	96.1	99.4	82.7	97.9	90.8	87.8
	1	10.3	12.4	24.8	31.1	43.9	49.7	13.2	66.1	31.0	84.9	10.6	66.6	17.5	24.0
	Overall[a]														
	All	96.1	96.0	96.7	96.8	97.1	97.2	96.3	97.6	96.9	98.0	96.1	97.6	96.5	96.5
	MRSA	92.1	91.9	93.3	93.3	94.0	94.2	92.6	94.8	93.5	95.7	92.1	94.8	92.8	92.9
	MSSA	99.1	99.1	99.3	99.3	99.5	99.5	99.2	99.6	99.4	99.8	99.1	99.6	99.2	99.2
1-$\log_{10}$ CFU reduction	0.25	96.9	93.1	99.7	98.5	99.7	99.4	98.3	99.8	99.4	99.9	96.3	99.3	98.5	96.8
	0.5	31.9	33.4	58.4	58.3	75.8	75.1	38.9	87.9	64.1	94.8	34.9	85.0	47.4	50.2
	1	0.33	1.07	1.00	4.40	5.33	11.8	0.67	22.5	2.40	46.6	0.40	28.3	1.18	3.86
	Overall[a]														
	All	94.4	94.2	95.3	95.3	95.8	95.9	94.7	96.5	95.4	97.1	94.4	96.5	94.9	94.9
	MRSA	88.9	88.5	90.6	90.5	91.6	91.7	89.4	92.8	90.9	94.0	89.0	92.8	89.9	89.9
	MSSA	98.5	98.5	98.8	98.8	99.0	99.0	98.6	99.2	98.9	99.5	98.5	99.2	98.7	98.7

Note: Shaded cells indicate percent probabilities of PK-PD target attainment by MIC ≥90%.
a. Based on data for 1,311 *S. aureus* isolates that were collected in the USA and Europe as part of the 2014 and 2015 SENTRY Antimicrobial Surveillance Program. Note, the MIC_{90} values for all *S. aureus* isolates and the MRSA (n=563) and MSSA (n=748) subsets based on these data were 0.25, 0.5, and 0.015 µg/mL, respectively.
b. Simulated patients received delafloxacin 200 mg IV q12h on Days 1-3 followed by 450 mg PO q12h on Day 4.

CONCLUSIONS

- The final population PK model for delafloxacin, which was used to carry out the simulations described herein, provided accurate and precise estimates of delafloxacin exposure.
- High percent probabilities of PK-PD target attainment (≥ 99.5%) were evident on Day 1 and after the PO switch on Day 4 at the MIC_{90} of 0.25 µg/mL for *S. aureus* across simulated patients with varying CLcr.
- These data, which provide support for delafloxacin dosing regimens for patients with ABSSSI, were used to support dosing recommendations provided in the package insert [5].

REFERENCES

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