Delafloxacin Population Pharmacokinetics and Covariate Exploration

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ABSTRACT

Background: Delafloxacin (DFX) is a broad spectrum quinolone with activity against methicillin-resistant *Staphylococcus aureus* being developed for the treatment of acute bacterial skin and skin-structure infections. A population PK (PPK) model was developed and covariate exploration was conducted for DFX using Phase 1 and 2 data.
Methods: Data were obtained from 8 studies: 4 (3 Phase 1, 1 Phase 2) used IV formulations and 4 (Phase 1) used PO formulations. A wide range of DFX doses were administered (50 to 1200 mg as single or multiple doses); no subjects received both IV and PO doses. PPK analyses were conducted using Monte-Carlo parametric expectation maximization (S-ADAPT 1.5.6). A PPK model for IV data was fit first followed by inclusion of the PO data. After the best PPK model was identified, covariate exploration was conducted on DFX $AUC_{0\text{-}24,ss}$ (for a maintenance regimen of 300 mg/day) using statistical models.
Results: The PPK dataset contained 9,716 plasma concentrations from 258 subjects. The final PPK model was a 2-compartment model with first-order absorption or zero-order infusion and parallel linear and nonlinear elimination. PPK parameters were assumed to be log-normally distributed; error variance models were additive plus proportional (separate models for IV and PO data). Core PPK parameter estimates were estimated with excellent precision (%SEM values of 2 to 6%); %CV in clearance parameters was moderate (30 to 60%); goodness-of-fit diagnostics indicated an unbiased fit to the data and an r^2 of 0.944 for observed vs individual fitted concentrations. Median (range) $AUC_{0\text{-}24,ss}$ was 22 (7.5 - 54) mg/L·h. Other than the route of administration (~15% lower exposure with PO), the only significant predictor of DFX $AUC_{0\text{-}24,ss}$ was body weight; average $AUC_{0\text{-}24,ss}$ decreased by ~40% over the weight range of 50 to 105 kg.
Conclusions: This PPK model for DFX, which fit the data well, has served as the basis for developing sparse PK sampling schemes and guiding dose selection for future clinical trials.

INTRODUCTION

- Delafloxacin (DFX) is an investigational fluoroquinolone distinguished by its excellent antibacterial activity against Gram-positive organisms including both methicillin-susceptible and –resistant *Staphylococcus aureus.*
- To date, several Phase 1 and 2 studies have been conducted as part of the development process for DFX.
- The objectives of these analyses were to develop a structural population pharmacokinetic (PPK) model for DFX using pharmacokinetic (PK) data from several studies and to examine the influence of patient-related factors on the PK of DFX.

METHODS

PK Data Collection and Assay

- Data were obtained from 8 studies: 4 (3 Phase 1, 1 Phase 2) used IV formulations and 4 (Phase 1) used oral formulations (PO).
- A wide range of DFX doses were administered (50-1200 mg).
- The determination of DFX in human plasma was performed by means of liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). Different assays had been used for the IV (conducted by Rib-X; LLOQ=0.005 µg/mL, inter-day CV%=15%) and oral studies (conducted by Abbott Labs; LLOQ=0.0077 µg/mL, inter-day CV%=13.3%).

Structural PPK Model Development

- Candidate PK models were fit to the DFX plasma concentration-time data using Monte-Carlo parametric expectation maximization (MC-PEM) as implemented in the open-source software program S-ADAPT [1].
- An iterative approach was taken in which the PK data from the IV studies was fit first followed by inclusion of the PK data from the PO studies.

METHODS

Structural PPK Model Development (Continued)

- Previous analyses had indicated that the clearance of DFX was potentially saturable. Thus, in addition to simple linear elimination, several permutations of capacity-limited models were evaluated.
- Interindividual variability (IIV) was initially modeled using an exponential model and an additive plus proportional error model was used to describe residual variability of PK data.
- Other structural models, IIV and/or residual variability error models were explored if these error models did not appear to adequately describe the observed data. Interoccasion variability (IOV) was introduced as necessary to explain intraindividual variability in select PK parameters.
- Model selection was based upon accepted criteria (Akaike's Information Criterion, diagnostic plots and precision).

Covariate Screening Analysis

- A PK simulation was conducted in which all subjects received a hypothetical regimen of DFX 300 mg once daily for 10 days. The dose-normalized, steady-state area under the concentration-time curve from 0 to 24 hrs ($AUCn_{0\text{-}24}$) was then estimated after the last dose by integrating the concentration-time curve.
- The $AUCn_{0\text{-}24}$ estimates were merged with the subject demographics (age, body weight (WT), body surface area (BSA), body mass index, sex), dose administration method, and baseline laboratory values (creatinine clearance (CLcr) and serum albumin) to assess the impact of these subject descriptors on the IIV in dose-normalized exposure.
- These data were then used to generate the univariable covariate screening plots and summary statistics.
- A multivariable linear regression model was then constructed to assess the statistical significance of any relationships apparent in the exploratory plots.

RESULTS

Data

- The final dataset contained 258 subjects and 9,716 plasma concentrations.
- 620 samples were BLQ and analyzed using the Beal M3 method [2]. None of the PK concentrations were determined to be outliers.
- All subjects underwent relatively intensive PK sampling with at least 10 plasma samples per subject.
- There were a total of 258 subjects in the dataset used for the covariate screening analysis; these represented a broad range of ages (median=29 yr, range=18-87) and body sizes (median WT=73 kg, range=52-106). CLcr estimates ranged from 50–160 mL/min/1.73 m^2.

PPK Model (Table 1)

- The most robust fit to the pooled data from the 8 studies was obtained with a two-compartment model with zero-order infusion or first-order absorption (following an absorption delay) and a mix of linear and non-linear elimination.
- IOV in total clearance and relative bioavailability improved the model fit.
- Separate residual error models were applied to the IV and PO data; the IIV was ~17% for the IV data and ~26% for the PO data.
- Precision of the population mean parameter estimates was excellent; %SEM values were all below 10% with the lone exception of lag time (%SEM=45%).
- Excellent fits to the data were obtained as evidenced by the overall r^2 of 0.944 (**Fig. 1, panel A**). In general, the other plots (**panels B, C, and D**) show reasonably consistent scatter about zero indicating that there were no significant biases in the fit of the data.

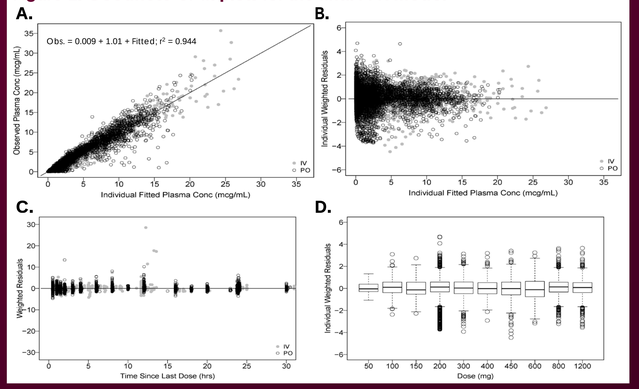
RESULTS

Table 1. Final PPK model — Final parameter estimates and standard errors

Parameter	Population mean		Magnitude of interindividual variability (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
Vc (L)	34.0	2.24	15.2	34.7
CLd (L/hr)	1.97	4.72	12.6	57.9
Vp (L)	22.5	5.66	12.6	83.5
CLi (L/hr)	4.16	4.35	14.5	56.8
Km (µg/mL)	0.963	4.30	19.5	45.2
CL_{lin} (L/hr)	10.5	1.99	16.0	28.8
Ka (L/hr)	1.03	5.81	15.5	66.4
F	0.863	3.65	32.6	15.3
Tlag	0.128	45.1	23.1	35.0
SD_{in}-IV	0.01	—	—	—
SD_{sl}-IV	0.170	2.13	—	—
SD_{in}-PO	0.01	—	—	—
SD_{sl}-PO	0.262	1.16	—	—
Minimum value of the objective function = -7691				

Note: IOV terms for F and CLt are not shown.
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; CL_{lin} is linear clearance; Ka is the first-order absorption rate constant; F is relative bioavailability; T_{lag} is lag time; SD_{in} is the intercept (additive) term for residual variability model for plasma concentrations; SD_{sl} is the slope (proportional) term for residual variability model.

Figure 1. Goodness-of-fit plots for the final PPK model



Covariate Screening Analysis

- Univariable screening plots indicated potential associations between $AUCn_{0\text{-}24}$ and route of administration, body weight, BSA and sex.
- Statistically significant predictors of the variability in exposure were route of administration and body size (body weight or BSA) (**Table 2** and **Fig. 2**).

RESULTS

Covariate Exploration

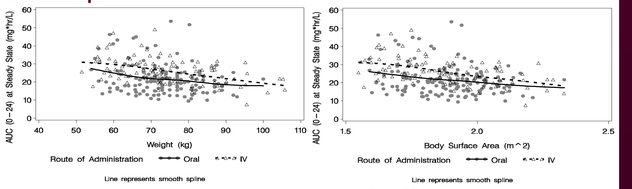
- Administration by IV infusion was associated with a ~20% increase in dose-normalized exposure; the effect of body size was such that the dose-normalized exposure would be predicted to decrease by 40-50% over the range of body sizes observed in the studies.

Table 2. Final multivariable linear regression models for factors predictive of dose-normalized $AUC_{0\text{-}24,ss}$

Parameter	Parameter estimate (standard error)	Wald P-value
	Model 1 (r^2 = 0.170)	
Intercept	21.6 (0.592)	<0.001
Weight (kg)[a]	-0.234 (0.0432)	<0.001
IV administration	4.50 (0.928)	<0.001
	Model 2 (r^2 = 0.178)	
Intercept	21.6 (0.589)	<0.001
BSA (m^2)[a]	-15.5 (2.73)	<0.001
IV administration	4.25 (0.924)	<0.001

a. Body weight and BSA were centered at their median values (73.8 and 1.89, respectively) prior to construction of the model.

Figure 2. Univariable scatterplots illustrating potential PK covariate relationships



Note: Lines are fitted, nonparametric smoothers (splines) through the IV and PO data separately.

CONCLUSIONS

- A two-compartment PPK model with a mix of linear and non-linear elimination provided an excellent fit to the pooled data from IV and PO studies.
- Overall, this model is expected to provide robust and reliable estimates of DFX PK exposure when used for pharmacokinetic-pharmacodynamic target attainment analyses.
- The covariate screening analysis, using dose-normalized exposure as a dependent variable, suggested that the variability in DFX PK was significantly associated with route of administration and body size.

REFERENCES

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