Population Pharmacokinetic Analysis for Intravenous and Oral Delafloxacin Using Data from Phase 1 Studies

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ABSTRACT

Background: Delafloxacin is an investigational IV and PO anionic quinolone being developed for acute skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). To assist with future dose selection assessments for CABP, the objectives of these analyses were to refine a previously-developed PPK model [ICAAC 2010, A1-682] and to explore covariates predictive of pharmacokinetic (PK) variability using pooled IV and PO data from Phase 1 studies.

Methods: PK data were obtained from healthy subjects and those with renal impairment after delafloxacin IV and PO (under fed and fasted conditions) administration. Delafloxacin daily doses ranged from 300 to 900 mg. Alterations to the structural model were evaluated and covariates (e.g., renal function, body size) associated with interindividual variability in delafloxacin exposure were explored.

Results: The analysis dataset contained 6211 plasma concentrations from 157 subjects with creatinine clearance (CLcr) ranging from 17.2 to 175.4 mL/min/1.73 m^2 and body weight (WTKG) ranging from 51 to 140.4 kg. A three-compartment model with mixed linear plus saturable elimination and two parallel first-order absorption processes provided unbiased estimates of delafloxacin exposure (r^2 = 0.902). Additionally, the good agreement between simulated and observed plasma concentrations from Phase 2 patients with ABSSSI after IV delafloxacin provided support for using this model to predict exposures for patients with CABP (**Figure 1**). Covariate analyses revealed 3 statistically significant relationships: 1) the linear portion of clearance decreased with decreasing baseline CLcr; 2) the volume of the central compartment increased with increasing WTKG; and 3) the absorption rate was slower after a high-fat meal compared to fasted conditions. Of these, only that for CLcr demonstrated a clinically meaningful effect on delafloxacin exposure (Figure 2).

Conclusions: The final PPK model provided precise fits to delafloxacin PK data after IV and PO administration in healthy subjects and patients with ABSSSI. CLcr exerted a clinically relevant influence on delafloxacin exposure. This model will be useful to assess delafloxacin dosing recommendations for patients with mild to severe renal impairment.

INTRODUCTION

- Delafloxacin is an intravenously (IV) and orally (PO) administered investigational quinolone with *in vitro* activity against a wide-spectrum of pathogens, including Gram-positive, Gram-negative, and atypical organisms.
- Given the *in vitro* activity against *Streptococcus pneumoniae* and MSSA and MRSA, delafloxacin is being developed for the treatment of patients with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI).
- The objectives of these analyses were to develop a structural population pharmacokinetic (PK) model for delafloxacin using PK data from four Phase 1 studies and to assess the impact of subject demographic characteristics and the effect of food on interindividual variability for selected PK parameters.

METHODS

Data

- Data were obtained from the four Phase 1 studies that are detailed in **Table1**.
- Extensive PK explorations were conducted to evaluate the PK characteristics of delafloxacin, including the following:
  - The impact of renal function on the delafloxacin exposure following single dose administration; and
  - The impact of food effects on the mean delafloxacin concentration-time profile in healthy volunteers.

Table 1. Summary of studies included in the delafloxacin population PK analyses

Protocol number	Study design	Dose regimens
RX3341-110	Randomized, crossover, single dose study in healthy volunteers or patients with renal impairment	300 mg IV or 400 mg PO
RX3341-114	Randomized, crossover, single dose study in healthy volunteers	400, 450, 475, 500 mg PO
RX3341-115	Randomized, single dose study in healthy subjects	300 mg IV or 450 PO mg or 900 mg PO
RX3341-116	Randomized, crossover, single dose study in healthy subjects	900 mg PO under fasting or fed conditions

METHODS

Population PK Model Development

- Candidate population PK models were fit to the pooled PK data using NONMEM® V7.1.2. All dataset creation and manipulation were performed using SAS® Version 9.3.
- The population PK model was developed in a sequential manner:
  - The IV data from Studies 110 and 115 were fit to a previously-developed population PK model (Rubino CM *et al.*, ICAAC 2010. Abstract No. A1-682.)
  - The model was fit to the pooled IV and PO data from all four studies to develop the final model.
  - Multi-compartment disposition model structures with simple and atypical absorption models were fit to the data.
- Covariate exploration involved graphical examination of plots of PK parameters versus demographic characteristics and food effects, using forward selection followed by a backward elimination procedure.
- Visual predictive checks (VPC) were used to evaluate the final model.

Monte Carlo Simulation

- To assess the impact of covariates on delafloxacin plasma exposures, simulated delafloxacin exposure based on the final PK model were examined in the following cohorts of simulated subjects (N = 500 for each cohort):
  - Reference subjects: Creatinine clearance (CLcr) of 120 mL/min/1.73 m^2 and weight of 70 kg under fasted conditions;
  - Mild, moderate and severe renal impairment: CLcr of 75, 45 and 20 mL/min/1.73 m^2 respectively, and weight of 70 kg under fasted conditions;
  - Overweight or low weight: Weight of 150 kg or 50 kg respectively, and CLcr of 120 mL/min/1.73 m^2 under fasted conditions;
  - Fed status : CLcr of 120 mL/min/1.73 m^2 and weight of 70 kg under fed conditions.
- For the cohort of reference subjects and cohorts with mild and moderate renal impairment, delafloxacin was given as 300 mg IV Q12h for 3 days followed by 450 mg PO Q12h for 2 days. For subjects with severe renal impairment, delafloxacin was also given as 200 mg IV Q12h for 3 days followed by 450 mg PO Q24h for 2 days.
- Results of these simulations are shown in the form of a forest plot.

RESULTS

Data

- The final analysis dataset for the development of the population PK model contained 6211 delafloxacin plasma concentrations from 157 subjects.
- The PK analysis population had a wide range of renal function (CLcr: 17.2 to 175 mL/min/1.73 m^2), and had a moderate range of weight distribution (51 to 140 kg).
- As shown in **Figure 1A**, PK data from Study 110 indicated that delafloxacin exposure increased with declining renal function, revealing renal function as a potential predictor of delafloxacin PK.
- As shown in **Figure 1B**, PK data from Study 116 indicated that plasma absorption was delayed by a high-fat/high calorie meal as displayed by the delayed time to peak concentration (T_{max}).

Population PK model

- The final population PK model for describing delafloxacin after IV and PO administration was a three-compartment model with mixed linear and non-linear (saturable) elimination, two parallel first-order absorption processes and an absorption delay for the second absorption process occurring through multiple transit compartments. Parameter estimates and associated standard errors are shown in **Table 2**.

RESULTS

Figure 1. Semilog plots of mean (SD) delafloxacin plasma concentration versus time since last dose profiles for subjects enrolled in Phase 1 Studies. Panel A shows mean profiles for subjects from Study 110, stratified by renal function. Panel B shows mean PK profiles for subjects from Study 116, stratified by fed status.

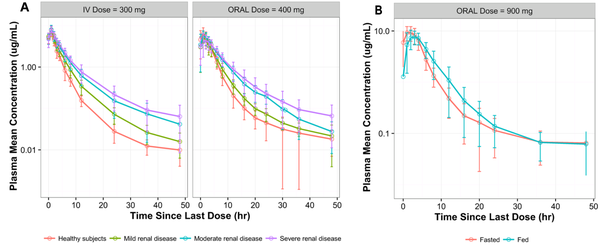


Table 2. Final population PK model parameter estimates and standard errors

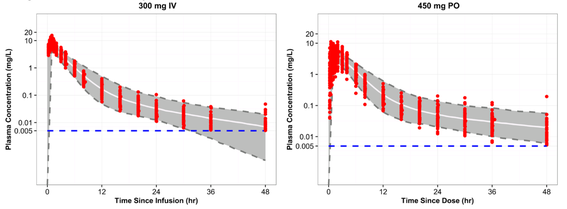
Parameter	Population mean		Magnitude of interindividual variability (%CV)	
	Final estimate	% SEM	Final estimate	%SEM
CL_{LN} (L/hr)	9.84	2.89	23.5	14.5
V_C (L)	17.5	3.42	13.4	52.2
Vmax (L/hr)	4.16	Fixed	14.5	Fixed
Km (µg/mL)	0.96	Fixed	19.5	Fixed
$Ka_{1(fasted)}$ (hr^{-1})	0.88	6.31	52.0	13.3
$Ka_{1(fed)}$ (hr^{-1})	0.41	5.88	52.0	13.3
Ka_2 (hr^{-1})	0.06	6.81	52.0	13.3
F_{TOT}	0.64	2.15	38.7	33.3
FS	0.06	8.64	76.2	20.7

CL_{LN}: linear clearance; V_C: volume of distribution; Vmax: maximum rate of Michaelis-Menten elimination from the central compartment; Km: concentration at which there is half-maximal Michaelis-Menten elimination from the central compartment; $Ka_{1(fasted)}$: immediate absorption rate constant in the fasted state; $Ka_{1(fed)}$: immediate absorption rate constant in the fed state; Ka_2: delayed absorption rate constant; F_{TOT}: total bioavailability; FS: fraction of delayed absorption bioavailability

- As shown by the VPC plots in **Figure 2**, there was good agreement between simulated delafloxacin plasma concentrations based on the final population PK model and observed plasma concentrations from healthy subjects in Study 115.
- Covariate analysis identified three statistically significant covariate relationships, which suggest the following:
  - Linear portion of clearance (CL_{LN}) increases with increasing CLcr;
  - Volume of central compartment (V_C) increases with increasing subject weight;
  - Absorption rate is faster under fasted conditions compared to the absorption rate after a high-fat/high calorie meal.
- Results of the Monte Carlo simulation evaluating the impact of covariates on delafloxacin exposure , which are shown in **Figure 3,** suggested the following:
  - Clinically significant increases in delafloxacin exposure, relative to the reference group, would be expected in subjects with severe renal impairment given the same dose
  - Based on the high degree of overlap in delafloxacin exposure among the overweight, under weight, and the reference group, the need for weight-based dosing recommendations are not likely.
  - The need for dose adjustments based on fed status does not appear to be needed based on the overlap in delafloxacin exposure between the fed group and fasted reference group.

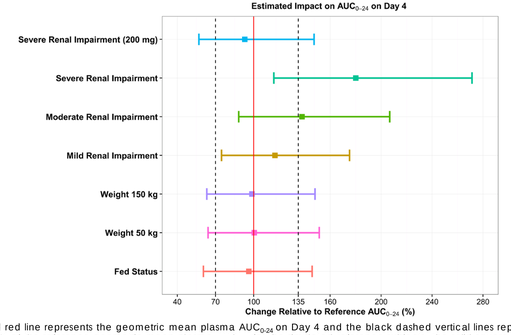
RESULTS

Figure 2. VPC plots of simulated and observed delafloxacin plasma concentrations from healthy subjects in Study 115 after administration of delafloxacin 300 mg IV or 450 mg PO, stratified by route of administration.



The solid line and grey shaded area represents the median and 90% CI, respectively, of model simulations for healthy subjects. The solid red dots represent the observed PK data while the blue dashed lines represent the lower limit of quantification.

Figure 3. Forest plot of covariate effects on delafloxacin plasma AUC_{0-24} on Day 4 after administration of delafloxacin.



The solid red line represents the geometric mean plasma AUC_{0-24} on Day 4 and the black dashed vertical lines represent 70 and 135% of the reference geometric mean plasma AUC_{0-24} for the simulated reference subjects. The solid square and error bars represent the geometric mean and 90% CI for the fold change of delafloxacin plasma AUC_{0-24} relative to the reference AUC_{0-24} for simulated subjects.

CONCLUSIONS

- Despite the variability in absorption profiles, a three-compartment model with parallel absorption and mixed linear and non-linear (saturable) elimination provided an adequate fit to delafloxacin plasma data at multiple dose levels in adult subjects after IV and PO administration.
- Population PK covariate model development resulted in the identification of three statistically significant covariate relationships which showed that linear clearance increases with increasing creatinine clearance, the volume of the central compartment increases with increasing subject weight, and the delafloxacin absorption rate is faster under fasted conditions.
- However, based on simulation results, the only covariate of clinical concern was renal impairment.