Extensive PK explorations were conducted to evaluate the PK characteristics of delafloxacin. Given the in vitro activity against Staphylococcus pneumoniae and MRSA, delafloxacin was being developed for 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 plasma data from four Phase 1 studies and to assess the impact of subject demographic characteristics and the effect of food on interindividual variability for fed vs. non-fed PK parameters.

METHODS

Population PK Model Development

- The population PK model was developed using NONMEM® version 7.3.2.1. All dataset creation and manipulation were performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC).

- The population PK model was developed in a sequential manner. The final analysis dataset for the development of the population PK model (Rubio CM et al., ICAAC 2013. Abstract No: A1-682) was used for the PK model development. A model was developed for each of the four studies to develop the final model.

- The model was fit to the pooled IV and PO data from all studies to develop the final model.

- The elimination compartment disposition model structures with single and explicit absorption models were fit to the data.

- Covariate exploration involved graphical examination of plots of PK parameters versus demographic, clinical, and food effects, for 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 exposures based on the final PK model were examined in the following cohorts of subjects: (i) 500 mL/min/1.73 m² and weight of 100 kg under fasted conditions; (ii) 80-year-old male renal impairment, delafloxacin was given as 300 mg IV Q12h for 3 days followed by 450 mg PO Q24h for 2 days for subjects with severe renal impairment, delafloxacin was also given as 200 mg IV Q24h 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

- As shown by the VPC plots in Figure 2, there was good agreement between simulated and observed plasma concentrations following the final population PK model and observed plasma concentrations from healthy subjects in Study 115. Covariance analysis showed that the population PK model for delafloxacin was a suitable predictor of delafloxacin PK.

Figure 1. Seeding plots of mean (± SD) delafloxacin plasma concentration time courses for the three groups of subjects evaluated. Panel A shows mean PK profiles for subjects from Study 110, stratified by fed status. Panel B shows mean PK profiles for subjects from Study 116, stratified by fed status.

Figure 2. VPC plots of simulated and observed delafloxacin plasma concentrations for 15 healthy subjects stratified by fed status. Panel A shows observed delafloxacin plasma concentrations following administration of delafloxacin in 300 mg or 450 mg PO, stratified by mode of administration.

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

Table 1. Final population PK model parameter estimates and standard errors

Table 2. Covariate data for delafloxacin plasma AUC_{0-24} on Day 4 after administration of delafloxacin

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