Population PK Modeling for Ceftazidime-Avibactam (CAZ-AVI) in Patients with Complicated Intra-abdominal Infection (cIAI) and Complicated Urinary Tract Infection (cUTI)

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Purpose
Avibactam (AVI) is a novel non-β-lactam β-lactamase inhibitor that restores the in vitro activity of β-lactams, including ceftazidime (CAZ), against Ambler class A, class C and some class D β-lactamase producing pathogens. CAZ, in the presence of AVI, has been shown to be active against otherwise CAZ-resistant bacterial strains that express a combination of β-lactamase types, as well as strains that are concomitantly resistant to other antibacterial classes such as fluoroquinolones. Phase 2 and 3 clinical studies have demonstrated the efficacy of CAZ-AVI for treatment of patients with cIAI or cUTI. The aim of this analysis was to develop population PK (PopPK) models of CAZ and AVI in patients with cIAI and cUTI from these Phase 2 and 3 studies.

Methods
Previously developed PopPK models for CAZ and AVI using data from patients with cIAI and cUTI in Phase 1 and 2 studies (Carrothers TJ et al. Presented at 5th American Conference on Pharmacometrics 2014, Las Vegas: Abstract T-071) were used as a starting point for the new dataset (pooled data from prior analysis and cIAI and cUTI data from Phase 3 studies). The first-order conditional estimation with interaction (FOCE-I) method in NONMEM was used for implementation of all PopPK modeling. All covariate effects, except for cIAI or cUTI patient population versus healthy volunteers, in the previous PopPK models were subjected to backward elimination to identify the base model with statistically significant covariates to carry forward for further model development. Clinically important covariates that were not included in the previous models were subsequently examined and included by a forward selection process. Model development was driven by data and based on various pre-specified goodness-of-fit indicators, including inspection of diagnostic and covariate scatter plots, precision of parameter estimates, the minimum objective function value, and prediction-corrected visual predictive checks of simulated and observed CAZ or AVI concentrations.

Results
The PopPK models for both CAZ and AVI were well described by a 2-compartment disposition model with between-subject variability for the population mean PK parameters of clearance (CL), volume of distribution of central compartment (Vc), and volume of peripheral compartment (Vp). Due to the scarcity of subjects with moderate or severe renal function, historical literature data for CAZ treatment in subjects with creatinine clearance (CrCl) <50 mL/min were used to augment the CAZ PK dataset allowing derivation of a relationship between CL and CrCl over the full range of renal function (from end stage renal disease (ESRD) to normal function). The primary covariates impacting CAZ PK were cIAI and cUTI population (versus healthy subjects), Japanese healthy subjects (versus non-Japanese healthy subjects), and body weight. However, the impact of covariates on CAZ exposure in Phase 3 patients with cIAI and cUTI with normal renal function compared to healthy subjects with normal renal function were relatively small (no greater than 30% and 20% for steady-state maximum concentration (Cmax) and area under concentration curve (AUC), respectively). The primary covariates impacting AVI PK were CrCl, renal function category of augmented renal clearance and ESRD, cIAI and cUTI population (versus healthy subjects), and body weight. The impact of covariates on avibactam exposure in Phase 3 patients with cIAI and cUTI with normal renal function compared to healthy subjects with normal renal function were small (less than 20% for both steady-state Cmax and AUC).

Conclusion
Overall, the predicted exposures (Cmax and AUC) are comparable in subgroups of Phase 3 patients with cIAI or cUTI for both CAZ and AVI, after including dose adjustment for subjects with renal impairment. Therefore, dose adjustment is not required for any covariates other than renal impairment. The population PK models describe the CAZ and AVI concentration data well and are suitable for the analysis of exposure-response and simulation of probability of PK/PD target attainment.