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Ceftazidime-avibactam population pharmacokinetic modelling and pharmacodynamic target attainment across adult indications and patient subgroups

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Conflict of interest

Jianguo Li and Shampa Das are former employees of and shareholders in AstraZeneca. Diansong Zhou is an employee of and shareholder in AstraZeneca. Mark Lovern, Michelle Green, Craig Comisar and Yuan Xiong are employees of Certara Strategic Consulting (formerly Quantitative Solutions), and James Wright is an employee of Wright Dose Ltd, both of which received funding from AstraZeneca for support and assistance with the population PK analyses. Merran MacPherson is a former employee of Wright Dose Ltd, and also holds shares in AstraZeneca. Joannellyn Chiu and Jeremy Hing are former employees of Certara Strategic Consulting. Todd Riccobene and Timothy J. Carrothers are employees of and shareholders in Allergan (formerly Actavis Inc, formerly Forest Laboratories).

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Abstract

Ceftazidime-avibactam is a novel β-lactam/β-lactamase inhibitor combination for the treatment of serious infections caused by resistant Gram-negative pathogens. Population pharmacokinetic (PK) models were built to incorporate PK data from five Phase III trials in patients with complicated intra-abdominal infection, complicated urinary tract infection or nosocomial (including ventilator-associated) pneumonia. Ceftazidime and avibactam PK were well-described by two-compartment disposition models, with creatinine clearance (CrCL) the key covariate determining clearance variability. Steady-state ceftazidime and avibactam exposure for most patient subgroups differed by ≤20% versus healthy volunteers. Probability of PK/pharmacodynamic target attainment (free plasma ceftazidime >8 mg/mL and avibactam >1 mg/mL for ≥50% of dosing interval) was ≥94.9% in simulations for all patient subgroups, including indication and renal function categories. No exposure-microbiological response relationship was identified because target exposures were achieved in almost all patients. These modelling results support the approved ceftazidime-avibactam dosage regimens (2000/500 mg every 8 hours, adjusted for CrCL ≤50 mL/min).

Introduction

There is an urgent need for new antimicrobial treatments to combat increasing antimicrobial resistance[1] among Gram-negative pathogens such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*, which are frequently involved in serious bacterial infections.[2-4] Avibactam is a first-in-class novel non-β-lactam β-lactamase inhibitor, which restores the *in vitro* activity of β-lactams, including ceftazidime, against Ambler class A, class C, and some class D β-lactamase-producing pathogens,[5-7] including those producing *Klebsiella pneumoniae* carbapenemase and OXA-48 carbapenemases, but not metallo-β-lactamases.[8-10] Ceftazidime-avibactam is approved in both the USA and Europe for the treatment of adults with cIAI ([complicated intra-abdominal infection] in combination with metronidazole), cUTI ([complicated urinary tract infection] including pyelonephritis), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP).[11, 12]

Ceftazidime-avibactam has been extensively studied in Phase II[13, 14] and III clinical trials in adult patients with cIAI (n=857) and cUTI (n=731), including in patients with infections caused by ceftazidime-non-susceptible organisms,[15-18] and in a Phase III trial in patients with nosocomial pneumonia (NP) including VAP (n=436).[19] These trials each included sparse pharmacokinetic (PK) sampling protocols, and these patient PK data were used to develop and update the ceftazidime and avibactam population PK (PopPK) models iteratively during clinical development.[20-22] Early models using data from healthy subjects and Phase II studies [20] were updated in subsequent iterations with Phase III data as these became available.[21, 22] Covariate effects were broadly consistent throughout the iterations and the main factors explaining variability in exposure of both ceftazidime and avibactam were patient population (patients versus healthy subjects) and creatinine clearance (CrCL), a surrogate for renal function.[20-22] Both ceftazidime and avibactam concentration-time courses were well-described by a linear two-compartment PK model. These early models were used in Monte Carlo simulations and probability of target attainment (PTA) analyses to support selection of ceftazidime-avibactam dosage regimens in Phase III trials, including in patients with various levels of renal function. The early models also supported the initial 2015 US Food and Drug Administration approval of ceftazidime-avibactam in cIAI and cUTI including pyelonephritis, thereby enabling an expedited approval pathway, which has subsequently been recognized by European regulatory authorities.[23, 24]

The PopPK analyses described here, which incorporate data from the ceftazidime-avibactam Phase III trials across all indications, evaluate the actual performance of the ceftazidime-avibactam dosage regimen used in these trials by (1) determining the impact of patient characteristics of potential clinical interest on ceftazidime and avibactam PK and (2) evaluating PTA against a range of pharmacodynamic (PD) targets in patients with cIAI, cUTI, and NP including VAP, and in different clinical scenarios, including various levels of renal function.

Methods

Analysis data and model construction

PopPK datasets were assembled for ceftazidime and avibactam using data from four Phase III cIAI or cUTI trials (RECLAIM 1 and 2 [analyzed as a single trial with one database],[15] and RECLAIM 3;[15, 16] RECAPTURE 1 and 2 [analyzed as a single trial with one database];[17] REPRISE[18]), one Phase III NP trial (REPROVE), two Phase II trials (cIAI;[13] cUTI[14]), and 11 Phase I trials. All trials were conducted in accordance with the Helsinki Declaration of 1975 (as revised in 1983) and approved by local/institutional ethics committees.

The datasets included healthy volunteers and patients, and the PopPK modelling utilized individual baseline covariate information, chronological records of serum creatinine (for CrCL calculations) and the full dosing and plasma sampling history. The range of estimated CrCL (Cockcroft-Gault equation) in the ceftazidime dataset was 8–488 mL/min. The avibactam dataset included subjects with normal renal function to end-stage renal disease (ESRD), as well as subjects with sepsis and augmented renal clearance (ARC, defined as measured CrCL ≥140 mL/min [8 h urine collection] and specific to study CXL-PK-04 [Table S1]); the estimated CrCL range was 11–610 mL/min.

Ceftazidime-avibactam plasma concentration-time data were analyzed using nonlinear mixed effects modelling, which in earlier PopPK analyses described the PK of both ceftazidime and avibactam as a two-compartment disposition model with first-order elimination from a central compartment following IV infusion, parameterized by CL, volume of the central compartment (V_c), inter-compartmental clearance (Q), and volume of the peripheral compartment (V_p).[22] The first-order conditional estimation with interaction (FOCE-INTER [FOCE-I]) method in NONMEM version 7.2 (Hanover, MD, USA) was used for model building. The previous models (including covariates) were run with the updated data set including patients from REPROVE, and the population effect for NP patients on V_c and CL was added. Outliers (conditional weighted residual error >4) were excluded prior to covariate model building. As the ceftazidime dataset lacked data for subjects with severe renal impairment, it was necessary to incorporate individual estimates of ceftazidime CL from patients with renal insufficiency reported in the literature into the base model (Supplementary Methods).

After covariate model building completion, which included assessment of additional covariates and refinement of previous covariate effects, different structures of the variance covariance matrix of random effects were evaluated. The final PopPK models were then rerun with and without outliers. Abnormally high ceftazidime concentrations (>750 mg/mL) were excluded from the final model. To further improve prediction of the observed data at the 10th percentile, the final models were re-estimated with the Stochastic Approximation Expectation Maximization method with Importance Sampling.

Selection of covariates

Covariate selection was performed using a forward-addition process followed by backward deletion (i.e. stepwise covariate model [SCM]). Covariates tested included: disease status/indication (e.g. NP, VAP or cIAI), ARC (specific to study CXL-PK-04 [Table S1], with subjects in other studies classified as non-ARC), markers of systemic disturbances (e.g. white blood cell [WBC] count ≤12000/μL, presence of fever, systemic inflammatory response syndrome or bacteremia, Acute Physiology and Chronic

Health Evaluation version II [APACHE II>10], sex, age, obesity status and body weight, race, CrCL/ESRD, dialysis, study phase, geographic region and NP with ventilation on the day of PK sampling (NPv, recorded as the presence of a ventilator in the hospital room, which includes patients with VAP or HAP who were ventilated on the day of PK sampling). The APACHE II score is an integrated measure of disease severity for intensive care patients, with higher scores signifying greater disease severity. Predicted mortality rises steeply for scores >10 (>10% mortality), and this represents a reasonable cut-off for defining more severely ill patients.[25] The effect on avibactam PK of concomitant administration of organic anion transporter 1 (OAT1) and OAT3 inhibitors (probenecid, cimetidine and diclofenac) was also evaluated, given that avibactam is a substrate for these transporters *in vitro*.[26]

Covariate effects with significance levels of p=0.01 during forward inclusion were carried forwards for backward elimination testing with an acceptance criterion of p=0.001. All covariates identified as being statistically significant during model building were subjected to clinical relevance criteria. Categorical covariates that resulted in <20% change relative to reference in the associated parameter, and continuous covariates that did not result in a ≥20% difference in the associated parameter at the 5th and/or 95th percentiles of the covariate relative to the covariate median, were generally deemed clinically irrelevant and dropped from the final model. Exceptions were made for covariates of particular clinical interest with <20% impact, or where the effect size was close to 20%.

Model evaluation

Standard diagnostic plots were used throughout model development to assess the ability of each model to describe the observed data, including observed versus individual (IPRED) and population (PRED) predicted concentrations, and weighted residuals (WRES)/conditional WRES/individual WRES versus PRED or time.

Bootstrap re-sampling techniques were used to evaluate the stability of the final model and to estimate non-parametric confidence intervals (CIs) for the model parameters. The same set of subjects as in the analysis dataset were used to generate 200 bootstrapped data sets. The median and 90% CIs of the PK parameter estimates fitted to these 200 resampled data sets were compared to the original PK estimates from the final model.

Visual predictive checks (VPCs) were used to evaluate the predictive performance of the final model. A prediction-corrected VPC (pcVPC) was performed using the VPC algorithm in Perl-speaks-NONMEM (PsN) v3.7.6. A total of 1,000 replicates (i.e. datasets) were simulated using the final models. Within each simulated replication the 10th, 50th and 90th percentiles of the simulated concentrations were computed by the nominal sampling time. By taking the 10th and 90th percentiles of the within-replicate statistic values, a 90% CI for each statistic was derived. Model performance was assessed based on the perceived congruence between the model-derived CIs and the observed data.

PK parameter calculations and simulations in Phase III patients

Empirical Bayes estimates of individual PK parameters for all Phase III subjects were used to derive secondary parameters e.g. maximum plasma concentration at steady state ($C_{max\ ss}$) and area under the plasma concentration-time curve at steady-state ($AUC_{ss,0–24}$). $C_{max,ss}$ and $AUC_{ss,0–24}$ for ceftazidime and avibactam were calculated for subgroups of clinical interest to verify acceptable exposure. Concentration-time courses of ceftazidime and avibactam were simulated for Phase III patients with ≥1 PK sample in the final PopPK datasets using observed CrCL taken closest to the PK sampling day (Day 3). These were used to calculate individual PK/PD target attainment in Phase III subjects as described below.

PK/PD targets

A joint PK/PD target for ceftazidime and avibactam was employed to assess the suitability of the Phase III dosage regimens. The joint target was defined as simultaneous achievement of 50% time (during each dosing interval) free plasma concentrations exceed ceftazidime-avibactam minimal inhibitory concentration (MIC) of 8 mg/L for ceftazidime (50% *f*T>8 mg/L), and 50% *f*T above a threshold concentration (C_T) of 1 mg/L for avibactam (50% *f*T>1 mg/L).[27] 50% *f*T>MIC is a an established PK/PD target for ceftazidime and other cephalosporins;[28-31] a target of 8 mg/L was chosen based on global surveillance studies where a ceftazidime-avibactam MIC of ≤8 mg/L was observed to include ≥90% of clinical isolates of *Enterobacteriaceae* and *P. aeruginosa*.[32-36] For avibactam, the PK/PD index was derived from hollow fiber and murine models of infection and determined as %*f*T>C_T.[37-39] In hollow fiber experiments using various strains of ceftazidime-resistant *Enterobacteriaceae* with fixed concentrations of ceftazidime and varying concentrations of avibactam, C_T values of 0.15 to 0.28 mg/L were sufficient to restore ceftazidime activity; when the concentration of avibactam was fixed in the presence of varying concentrations of ceftazidime, a C_T ≤0.5 mg/L restored the activity of ceftazidime.[37] In neutropenic mouse thigh and lung infection models using various strains of ceftazidime-resistant *P. aeruginosa*, %*f*T>1 mg/L values of approximately 16–24% were associated with stasis, and values of approximately 20–55% were associated with $2\log_{10}$ reductions in bacterial denisty.[38] Accordingly, the avibactam target C_T value for both *Enterobacteriaceae* and *P. aeruginosa* was set to 1 mg/L.[27]

The joint PK/PD target was applied to the predicted PK profiles in Phase III patients to determine individual target attainment, and was also used in PTA simulations. There was no relationship between C_T and MIC for any of the bacterial strains tested.[37-39] However, to further explore the performance of the Phase III ceftazidime-avibactam dosage regimens, a sensitivity analysis of more conservative joint PK/PD targets was also evaluated in PTA simulations.

Exposure-response analysis

PK target attainment analyses used free plasma concentrations (taken to be 85% and 92% of total plasma concentrations for ceftazidime and avibactam, respectively). To explore exposure-response relationships by indication, estimates of %*f*T>MIC ceftazidime, %*f*T>MIC ceftazidime-avibactam, and %*f*T>C_T for avibactam, were calculated from simulated ceftazidime and avibactam profiles. %*f*T>MIC (2, 4, and 8 mg/L) for ceftazidime and %*f*T>C_T (0.5, 1, 2, and 4 mg/L) for avibactam were also

estimated to explore fully target attainment for the approved doses using a range of targets beyond those determined from nonclinical studies. Logistic regression of overall microbiological response (OMR) as a function of each exposure metric was conducted for patients with both baseline MIC data and ceftazidime and avibactam exposure metrics. In addition to the above dichotomous targets, a continuous endpoint, defined as %*f*T >MIC COR, was also evaluated for its potential utility in predicting clinical outcome. MIC COR is an avibactam-corrected ceftazidime MIC calculated as a function of the avibactam concentration and the MIC of ceftazidime against a pathogen evaluated in the presence and absence of 4 mg/L avibactam, and fluctuates over time in conjunction with avibactam exposure.

Exposure and PTA simulations

PTA simulations were based on the final PK models for ceftazidime and avibactam developed using pooled data from the Phase III RECLAIM, REPRISE, RECAPTURE and REPROVE trials. To account for the correlation between ceftazidime and avibactam random effects, the random effects were bootstrapped using the approaches detailed in the supplement. To avoid any bias in PTA caused by shrinkage towards the median of post-hoc parameters and ensure the results were conservative, the random effects were inflated by a factor inversely proportional to the estimated shrinkage.

PTA simulations were conducted for 5,000 simulated patients for each indication and renal function group. Covariate records for 5,000 simulated patients were obtained by sampling with replacement from Phase III patients in each population that had normal renal function on the PK day (i.e. CrCL >80 mL/min). Simulations incorporated covariate distributions appropriate to each patient population and between-patient variability, but excluded residual error and uncertainty in the population parameters. For cIAI, simulations were performed for all patients, Chinese patients, and non-Chinese, non-Japanese Asians. For NP, simulations were for all NP patients, only patients with VAP, only non-VAP patients, and only NPv patients. Simulations were also performed for cUTI, NP including VAP, non-VAP and NPv for Chinese patients and/or non-Chinese, non-Japanese Asians. Simulations of patients with renal impairment were for label-recommended dosage adjustments by category, and CrCL values were assumed to follow a uniform distribution within the designated range for each category.

Results

Analysis populations

An overview of the clinical studies included in the PopPK models is provided in Table S1. The final ceftazidime dataset included 9,155 observations from 1,975 adult subjects: 86 healthy subjects (4.4%), 696 cUTI patients (35.2%), 781 cIAI patients (39.5%) and 412 (20.9%) NP patients. The final avibactam dataset included 13,735 observations from 2,249 subjects: 345 healthy subjects or subjects with renal impairment from Phase I studies (15.3%), 705 cUTI patients (31.3%), and 786 cIAI patients (34.9%) and 413 NP patients (18.4%). Demographic data are summarized in Tables S2 and S3.

Final population PK models

The ceftazidime and avibactam PopPK data were well-described by a two-compartment disposition model. Parameter estimates from the final models are shown in Tables 2 and 3; equations for the covariate relationships are in the Supplementary Results. Parameter estimates from the full analysis datasets differed from the median bootstrap estimates by <20% except for intercompartmental clearance for ceftazidime, and the parameter estimates from bootstrapping were within the CIs (Tables S4 and S5). PcVPCs (Figures 1, 2, and S1–S8) demonstrated that the final models reflected the observed data and were suitable for use in simulations. Goodness-of-fit plots for ceftazidime and avibactam (Figures S9 and S10) showed that the models exhibited minimal bias.

Ceftazidime

CrCL was the key covariate predicting ceftazidime CL (Table 1). The relationship was close to proportional at CrCL<100 mL/min; for CrCL≥100 mL/min the regression slope of ceftazidime CL versus CrCL was very shallow (12.5% increase in CL per 100 mL/min increase in CrCL above 100 mL/min). No other covariate effects on CL in Phase III patients exceeded the predefined threshold for clinical relevance (±20%). Noteworthy small covariate effects on ceftazidime CL that were retained in the final model (as exceptions to the general rule) were indication (16% higher CL for cIAI patients versus healthy subjects and cUTI patients) and racial/regional origin (Chinese patients had 9% lower CL and non-Chinese, non-Japanese Asians 16% lower CL than non-Asians).

The covariate effects on ceftazidime Vc that were included in the final model were: indication/indication subgroups, Asian race, body weight, pyelonephritis and NPv (Table 1). Estimated effects exceeding ±20% were: a 27% lower V_c for Asian compared with non-Asian patients; a 29.7% higher V_c for NPv patients than for non-NPv patients; a 24% lower and 26% higher V_c for patients with body weight at the 10th percentile (50 kg) and 90th percentile (94 kg), respectively, compared with those of median weight (70 kg).

All fixed effect parameters were estimated with good precision, with all relative standard errors (RSEs) <27% except for the effect of acute pyelonephritis on V_c (41.2%) and the effect of NPv on V_c (45.4%). Inter-individual random effects with a correlation parameter estimated between CL, V_c, V_p and Q were also well estimated, with %RSEs generally <16%.

Avibactam

CrCL was the key covariate predicting the CL of avibactam (Table 2). For patients with CrCL <80 mL/min, CL dependence on CrCL was estimated as a power function of 1.05 indicating an approximately linear relationship. For patients with CrCL ≥80 mL/min, the relationship between CL and CrCL was modelled as a shallow linear function such that avibactam CL increased by 27.9% for an increase of 100 mL/min in CrCL over 80 mL/min. For ESRD patients, CL was 0.0678 L/h off dialysis and 20.8 L/h on-dialysis. The largest covariate effect on CL in Phase III patients aside from renal function was a 19.7% decrease for APACHE II score >10. Also noteworthy was an estimated 8.65% lower CL (translating to a 9.5% increase in AUC) for non-Chinese, non-Japanese Asians compared with that for patients of other racial origins and this covariate was also retained in the final model.

The covariate effects on avibactam V_c that were retained in the final model and relevant to Phase III subjects were body weight, indication, and NPv status (Table 2). Subjects at the 10th (51 kg) or 90th percentile of body weight (95 kg) had estimated V_c respectively 29% lower or 39% higher than the median weight (70 kg). The V_c was 32.9% and 43.4% higher for Phase III cIAI and NP patients and cUTI patients, respectively compared with healthy subjects. NPv patients had estimated V_c 17.5% higher than non-NPv patients. All fixed effect parameters were estimated with good precision, with %RSEs generally <29%, except for the NPv effect on V_c (53.3%). Inter-individual random effects, with correlation parameters estimated between CL, V_c, V_p and Q were also well estimated, with all %RSEs <18%. Correlation between some of the random effect parameters was high ($-0.36 < r^2 < 0.99$).

Exploratory exposure-response analysis

The exposure-response analyses included 359 cIAI patients, 420 cUTI patients and 124 NP patients who had one or more aerobic Gram-negative pathogen isolated at baseline. Almost all individual ceftazidime %*f*T>MIC ceftazidime-avibactam and avibactam %*f*T >C_T values were close to 100%. The low treatment failure rates in the Phase III trials limited investigation of clinical PK/PD relationships, and no meaningful exposure-response relationships were observed. Higher avibactam C_T targets and C_T targets corrected for MIC in the presence and absence of avibactam were investigated as an exploratory analysis; again, there were no meaningful exposure-response relationships noted. Unfavorable OMR was relatively infrequent among cIAI and cUTI patients (5.8% and 15.5% respectively) but more prevalent among NP patients (38.7%).

Individual predicted exposures and joint PK/PD target attainment in Phase III patients

Ceftazidime exposures were similar in cUTI and NP patients, and lower in cIAI patients (up to 23.0% lower $AUC_{ss,0–24}$; Table 3). Avibactam exposures were similar in cUTI and cIAI patients and higher in NP patients (up to 28.0% higher $AUC_{ss,0–24}$). VAP patients had approximately 20% lower $AUC_{ss,0–24}$ and $C_{max,ss}$ for both ceftazidime and avibactam than non-VAP patients, reflecting their higher V_c and CrCL. Actual joint PK/PD target attainment rates (50% *f*T>8 mg/L for ceftazidime and 50% *f*T>1 mg/L for avibactam) were >97% for cIAI, cUTI and NP, including VAP and non-VAP subgroups (Table 3). Joint target attainment rates were >93% across all other evaluated subgroups, except for the 8–15 mL/min renal function group (n=4), which was too small for meaningful comparison (Table 3). Exposure and joint target attainment rates were comparable among patients with and without baseline bacteremia, APACHE II score >10, SIRS at baseline, fever at baseline, or concomitant use of OAT1/OAT3 inhibitor(s), with $C_{max,ss}$ and $AUC_{ss,0–24}$ differing by ≤25%. Age- or obesity-related changes in exposure appeared to be adequately captured by changes in CrCL. For high CrCL, $AUC_{ss,0–24}$ decreased, however, joint target attainment remained >95% in the 150–180 mL/min and 180–395 mL/min subgroups, reflecting the relatively small increases in ceftazidime and avibactam clearance at higher CrCL. Japanese patients had higher ceftazidime and avibactam exposure than the Caucasian/Other reference population and achieved 100% joint target attainment.

Exposure and PTA simulations

For simulated patients with normal renal function (CrCL >80 mL/min), geometric mean exposure parameters for ceftazidime differed by <10% in the cIAI, NPv, and VAP populations. Compared with cIAI patients, ceftazidime geometric mean $C_{max,ss}$ and $AUC_{ss,0–24}$ were 19% and 29% higher for cUTI patients, respectively, and 24% and 31% higher for non-VAP patients, respectively (Table 4). Simulated avibactam exposure parameters differed by <10% across cIAI, cUTI, NPv and VAP patient populations with normal renal function (Table 4). Non-VAP patients had higher avibactam exposures, with geometric mean $C_{max,ss}$ and $AUC_{ss,0–24}$ 28% and 36% higher, respectively, than cIAI patients (Table 4). For NP patients overall, avibactam $C_{max,ss}$ and $AU_{Css,0–24}$ were 11% and 21% higher, respectively, than for cIAI patients, reflecting the contribution of the non-VAP subset.

Across all indications, patients with mild renal impairment (CrCL 51 to <80 mL/min) had higher predicted ceftazidime and avibactam exposure parameters than those with normal renal function receiving the same dose (Table 4). Patients with moderate (CrCL 31 to <50 mL/min) or severe (CrCL 6 to <30 mL/min) renal impairment receiving the appropriate label dose adjustments had lower predicted ceftazidime and avibactam $C_{max,ss}$ than those with normal renal function, while maintaining slightly higher $AUC_{ss,0–24}$. In dose-adjusted patients with ESRD, simulated ceftazidime $C_{max,ss}$ and $AUC_{ss,0–24}$, were 139–156% and 220–238%, respectively higher than in patients with normal renal function; for avibactam these values were 80–87% and 101–111%, respectively higher. Simulations for the ESRD population did not account for drug removal through hemodialysis, hence these high exposures represent a worst-case scenario. PTA simulations demonstrated that PTA exceeded 94.9% at a ceftazidime-avibactam MIC of 8 mg/L across all indications and renal function subgroups (Table 4). Joint PTA plotted as a function of ceftazidime-avibactam MIC in simulated cIAI, cUTI and NP patients with normal renal function is shown in Figure 3. >90% PTA was maintained for more joint stringent targets up to 60% *f*T>8 mg/L for ceftazidime and 60% *f*T>1 mg/L for avibactam (data not shown).

Discussion

PopPK modelling of antimicrobial therapies, and simulations for PTA analysis, are recognized techniques for optimizing dosing for efficacy and safety.[40, 41] They also play a role in the determination of interpretative criteria (breakpoints), particularly when pathogens isolated in clinical studies have a limited range of MICs.[42]

These PopPK models for ceftazidime and avibactam described well the PK of both drugs in Phase III cIAI, cUTI and NP patients. The main factors influencing variability in exposure of both avibactam and ceftazidime, primarily renal function, were well-characterized. The final models were qualified using VPCs and deemed suitable for use in PTA simulations. Major strengths of the modelling include the inclusion of a high proportion of patient PK data, the inclusion of subjects with renal function varying from ARC to ESRD, and the comprehensive set of covariates examined. Ceftazidime and avibactam are predominately excreted by the kidneys, so understanding the effects of reduced and augmented renal function on exposure is vital. Examining covariates relating to critical illness and septic shock was also important because these can significantly affect the volume of distribution and exposure of many other antimicrobial agents.[43-46]

The PopPK models accurately predicted exposure in patients with varying degrees of renal function: clearance of both avibactam and ceftazidime was close to proportional at CrCL <80 mL/min and <100 mL/min respectively, and at higher CrCL values, drug clearance increased only modestly with increasing CrCL. Comparison of the model-predicted $AUC_{ss0–24}$ between Phase III patients across all indications with normal renal function and those with mean estimated CrCL >150 mL/min showed that small reductions in ceftazidime and avibactam exposure in patients with high CrCL had no impact on target attainment rates, which were >95.7%. These data confirm the final dosing recommendations using exposure and PTA data from all Phase III trials,[47] and indicate that dose adjustments are only necessary for patients with CrCL <50 mL/min, in whom clearance of ceftazidime and avibactam is appreciably reduced; dose adjustments are not warranted for patients with ARC.

In Phase III patients, individual target attainment at a ceftazidime-avibactam MIC of 8 mg/L exceeded 97% in all indications, as well as other subgroups of potential clinical significance including obesity, SIRS, fever, elevated WBCs, concomitant OAT1/OAT3 inhibitors and bacteremia. This reflects the limited impact of covariates other than CrCL on ceftazidime and avibactam exposure, and demonstrates that the ceftazidime-avibactam dosage regimen of 2000-500 mg q8h for patients with CrCL >50 mL/min provides appropriate plasma concentration profiles for nearly all patients, including those with severe systemic disturbances, advanced age, high CrCL and obesity.

In PTA simulations using the updated PopPK models, the proposed ceftazidime-avibactam regimens, including dose adjustments for renal impairment, provided PTA >90% in every patient subgroup studied in Phase III across cUTI, cIAI and NP (including HAP and VAP) indications. PTA simulations were performed using re-inflated post-hoc PK parameters to account for shrinkage, which is a more conservative approach than generally applied. In addition, calculations were based on a robust joint target, providing a high degree of confidence that both ceftazidime and avibactam will reach required plasma concentrations. A >90% PTA for the joint PK/PD target of ≥50% *f*T>8 mg/L for ceftazidime and ≥50% *f*T>C_T of 1 mg/L for avibactam supports a ceftazidime-avibactam MIC breakpoint of 8 mg/L against both *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Of note, the modelling of β-lactam/β-lactamase inhibitor combinations is an evolving field with various approaches being adopted by the sponsors of different recently developed combinations and those currently in investigation. Our approach involved defining fixed joint PK-PD targets that were conservative with respect to the exposure levels assumed to be required for clinical efficacy. Other investigators have started to develop mechanistic-based modelling approaches, including for the ceftazidime-avibactam combination.[48-50]

In conclusion, PopPK models of ceftazidime and avibactam incorporating Phase III data from patients with cIAI, cUTI, and NP, found several covariates influence variability in exposure to both agents. However, CrCL was the only covariate with a sufficiently large effect to warrant dose adjustments. These analyses provide confidence that the approved ceftazidime-avibactam dosage regimens (including adjustments for CrCL ≤50 mL/min), provide sufficient exposures for patients with all approved indications and across a range of clinical circumstances considered challenging for other antibiotics, such as bacteremia, SIRS, obesity, ARC, and mechanical ventilation.

Study highlights

What is the current knowledge on the topic?
PopPK models of ceftazidime and avibactam in patients with complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI) which showed that creatinine clearance is the key covariate determining clearance were used to support dose selection and adjustments for patients with renal impairment in Phase III trials.

What question did this study address?
What is the impact of different patient covariates and infections/site of infections, including nosocomial pneumonia, bacteremia and augmented renal clearance, on ceftazidime and avibactam PK and on the probability of pharmacodynamic target attainment?

What does this study add to our knowledge?
PTAs derived from population PK modelling incorporating data from Phase III trials were >90% across all indications (cIAI, cUTI including pyelonephritis and nosocomial pneumonia including ventilator-associated pneumonia) and patient subgroups, and supported an MIC breakpoint of 8 mg/L against *Enterobacteriaceae* and *Pseudomonas aeruginosa.*

How might this change clinical pharmacology or translational science?
These analyses demonstrate the value of population PK models and joint PTA simulations to guide combination drug (e.g. antibiotic and inhibitor) development decisions.

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Author contributions

All authors wrote the manuscript; J.L., D.Z., T.R., T.J.C., and S.D. designed the research; J.L., M.L., M.L.G., J.C., D.Z., C.C., X.Y., J.H., M.M., J.G.W., T.R., T.J.C., and S.D. performed the research; M.L., M.J.L., J.C., C.C., X.Y., and J.H. analyzed the data.

Data sharing

Upon request, and subject to certain criteria, conditions and exceptions see (https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider

requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Figure legends

Figure 1. Prediction-corrected visual predictive check stratified by population for ceftazidime

Solid lines represent medians and 10th and 90th percentiles of observed data. Shaded regions encompass 90% of the simulated (n=1000) values of the predicted medians (red) and 10th and 90th percentiles (blue) Data points represent the observed data (ng/mL)

CI, confidence interval; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; non-VAP, not ventilator-associated pneumonia; NP, nosocomial pneumonia; Obs, observations; VAP, ventilator-associated pneumonia

Figure 2. Prediction-corrected visual predictive check stratified by population for avibactam

Solid lines represent the median of the observed data. Shaded regions encompass 90% of the simulated (n=5000) values of the predicted medians, 5th, and 95th percentiles. Data points represent the observed data (ng/mL)

AVI, avibactam; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; non-VAP, not ventilator-associated pneumonia; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia

Figure 3. Simulated joint PTA as function of ceftazidime-avibactam MIC in 5000 simulated cIAI, cUTI or NP patients with normal renal function receiving ceftazidime-avibactam 2000-500 mg every 8 hours

cIAI, complicated intra-abdominal infection; MIC, minimum inhibitory concentration; NP, nosocomial pneumonia; PTA, probability of target attainment

Joint target attainment was defined as 50% fT >8 mg/L for ceftazidime, and 50%fT >1 mg/L for avibactam

Supplementary file titles

Supplemental material

Model code file

Table 1. Parameter estimates for the final ceftazidime population PK model

Parameter (units)	Estimate	%RSE	BSV (CV%)
Slope1: CrCL <100 mL/min, slope1*CrCL	0.0103036	0.409	NA
Slope2: CrCL ≥100 mL/min, slope1*100 + slope2*(CrCL–100)	0.001252	8.84	NA
θ_1: CL (L/h)	6.95	1.7	42.3
θ_2: V_c (L)	10.5	13.1	105
θ_3: Q (L/h)	31.5	18.8	259
θ_4: V_p (L)	7.57	9	110
θ_5: Population effect on CL (cIAI)	1.16	2.2	NA
θ_6: Population effect on CL (NP)	0.999	2.4	NA
θ_7: Race effect on CL (ASN)	–0.161	11.8	NA
θ_8: Race effect on CL	–0.0855	27	NA
θ_9: Population effect on V_c (cUTI)	1.03	11.1	NA
θ_{10}: Population effect on V_c (cIAI or NP)	1.14	9.9	NA
θ_{11}: Population effect on V_c (cUTI/acute pyelonephritis)	–0.185	41.2	NA
θ_{12}: Race effect on V_c (ASN, CHN, JPN)	–0.27	18.6	NA
θ_{13}: WT effect on V_c	1.01	12.6	NA
θ_{14}: Population effect on V_c (NPv)	0.297	45.4	NA
			Shrinkage (%) or correlation[†]
ηCL^2	0.179	3.3	11.4
ηV_c^2	1.10	10.2	31.2
-ηV_c -ηCL covariance[‡]	–0.189	15.2	r = –0.42
ηV_p^2	1.21	8.8	17.5
ηV_p -ηCL covariance[‡]	0.383	5.1	r = 0.82
ηV_p -ηV_c covariance[‡]	–0.972	7.3	r = –0.84

ηQ^2	6.70	15.5	27.46
ηQ -ηCL covariance‡	0.883	10.1	r = 0.81
ηQ -ηV_c covariance‡	–0.643	43.1	r = –0.24
ηQ-ηV_p covariance‡	1.73	14.5	r = 0.61
Residual noise			
Proportional error, Phase I‡	0.04	0.5	2.9
Additive error, Phase I‡	26489	7.5	2.9
Proportional error, Phase II and Phase III‡	0.114	2.1	9.5
Additive error, Phase II and Phase III‡	18.4	447	9.5

†Correlation coefficient (r) between random effects; ‡Reported as variance.

ASN, non-Japanese, non-Chinese Asian; BSV, between-subject variability; CHN, Chinese; cIAI, complicated intra-abdominal infection; CL, clearance; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; %CV, coefficient of variation; JPN, Japanese; NA, not assessed; NP, nosocomial pneumonia; NPv, nosocomial pneumonia with the presence of a ventilator in the hospital room on the day of pharmacokinetic sampling, which includes ventilator-associated pneumonia and hospital-acquired pneumonia in patients who were receiving ventilation on the day of sampling; Q, inter-compartmental clearance; %RSE, % relative standard error; Vc, volume of the central compartment; Vp, volume of the peripheral compartment; WT, body weight.

Table 2. Parameter estimates for the final avibactam population PK model

Parameter (units)	Estimate	%RSE	BSV (CV%)
θ_1: CL (L/h)	10.2	1.8	59.1
θ_2: V_c (L)	11.1	9.9	107.1
θ_3: Q (L/h)	5.44	13.9	122.2
θ_4: V_p (L)	6.91	6.5	252.2
θ_5: CL estimate for ESRD patients	0.0678	8.3	NA
θ_6: CL estimate for dialysis patients	20.8	9.6	NA
θ_7: Power CrCL (<80) on CL	1.05	2.4	NA
θ_8: Linear CrCL (≥80) on CL	0.00279	3.7	NA
θ_9: Population effect on V_c (cIAI, Phase II), $V_c*(1+\theta_9)$	1.92	25.4	NA
θ_{10}: Population effect on CL (cIAI, Phase II), $CL*(1+\theta_{10})$	0.406	23.2	NA
θ_{11}: Population effect on V_c (cUTI), $V_c*(1+\theta_{11})$	0.434	24	NA
θ_{12}: Population effect on V_c (cIAI, Phase III, NP), $V_c*(1+\theta_{11})$	0.329	28.6	NA
θ_{13}: Scaling factor for CrCL in subjects with ARC, $CL=TVCL*(1+\theta_8*\theta_{13}*$ [CrCL–80])	0.992	17.4	NA
θ_{14}: WT on V_c $(WT/70.0)^{\theta 14}$	1.08	7.8	NA
θ_{15}: APACHE II on CL, $CL*(1+\theta_{15})$	-0.197	8.7	NA
θ_{22}: ASN on CL, $CL*(1+\theta_{22})$	-0.0865	20.2	NA
θ_{28}: NPv on V_c ,$V_c*(1+\theta_{28})$	0.175	53.3	NA
			Shrinkage (%)[†]
ηCL^2	0.349	2	7.29
ηV_c^2	1.147	6	28.15
ηV_c -ηCL[‡]	0.125	15.6	r = 0.2
ηV_p^2	1.494	7	13.52
ηV_p -ηCL[‡]	0.611	3.6	r = 0.85
ηV_p -ηV_c[‡]	–0.426	18	r = –0.33
ηQ^2	6.359	8.1	14.18
ηQ -ηCL[‡]	1.231	4.1	r = 0.83
ηQ -ηV_c[‡]	–0.978	16.8	r = –0.36
ηQ-ηV_p[‡]	3.059	7.1	r = 0.99

Residual noise			
θ_{17}: Proportional error, Phase I	0.173	0.1	NA
θ_{18}: Additive variability, Phase I	44.6	0.5	NA
θ_{19}: Proportional variability, Phase II	0.492	3	NA
θ_{20}: Proportional variability, Phase III	0.363	1.1	NA

[†]Correlation coefficient (r) between random effects; [‡]Reported as variance.

ARC, augmented renal clearance; ASN, non-Japanese, non-Chinese Asian; BSV, between-subject variability; CHN, Chinese; CI, confidence interval; cIAI, complicated intra-abdominal infection; CL, clearance; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; %CV, coefficient of variation; ESRD, end-stage renal disease; JPN, Japanese; η, individual random subject effect; NA, not assessed; NP, nosocomial pneumonia; NPv, nosocomial pneumonia with the presence of a ventilator in the hospital room on the day of pharmacokinetic sampling, which includes ventilator-associated pneumonia and hospital-acquired pneumonia in patients who were receiving ventilation on the day of sampling; θ, typical value of pharmacokinetic parameter; Q, inter-compartmental clearance; %RSE, % relative standard error; Vc, volume of the central compartment; Vp, volume of the peripheral compartment; WT, body weight.

Table 3. Individual predicted ceftazidime and avibactam steady-state exposures and joint PK/PD target attainment for subgroups of actual Phase III cIAI, cUTI and NP patients

	n	Ceftazidime		Avibactam		Joint PK/PD target attainment rate, % (95% CI)[†]
		$C_{max,ss}$ geometric mean (CV), mg/L	$AUC_{ss,0-24}$ geometric mean (CV), m·h/L	$C_{max,ss}$ geometric mean (CV), mg/L	$AUC_{ss,0-24}$ geometric mean (CV), m·h/L	
Patient population						
cUTI	648	77.9 (114.2)	979 (119.7)	12.1 (161.9)	138 (164.1)	98.5 (97.5, 99.4)
cIAI	703	66.9 (105.0)	749 (114.0)	12.8 (155.3)	132 (152.0)	98.6 (97.7, 99.5)
NP	413	72.9 (125.2)	950 (131.0)	14.2 (166.1)	169 (168.5)	99.0 (98.1, 100.0)
Non-VAP	275	79.0 (120.0)	1016 (122.0)	15.5 (166.9)	183 (168.7)	99.6 (98.9, 100.0)
VAP	138	61.9 (127.0)	830 (142.7)	12 (157.6)	146 (163.0)	97.8 (95.4, 100.0)
Bacteremia at baseline						
No	1465	71.9 (116.1)	881 (125.5)	12.6 (157.3)	141 (161.2)	98.6 (98.0, 99.2)
Yes	88	73.6 (102.8)	919 (120.1)	14.2 (164.1)	161 (161.3)	100.0 (NA)
Baseline APACHE II score						
≤10	677	67.0 (105.0)	748 (113.8)	12.7 (154.3)	131 (150.6)	98.5 (97.6, 99.4)
>10	438	72.3 (124.3)	938 (130.9)	14.3 (167.0)	170 (168.7)	99.1 (98.2, 100.0)
Missing[‡]	649	77.9 (114.1)	979 (119.7)	12.1 (161.8)	138 (164.0)	98.5 (97.5, 99.4)
SIRS at baseline						

No	770	72.3 (108.9)	895 (120.5)	12.8 (159.2)	143 (162.0)	99.1 (98.4, 99.8)
Yes	773	71.5 (121.3)	869 (129.7)	12.6 (157.1)	142 (161.3)	98.3 (97.4, 99.2)
Missing	10	83.5 (130.2)	977 (123.7)	12.1 (115.1)	129 (116.4)	100.0 (NA)
Baseline WBC count (cells/µL)						
≤12000	876	74.6 (110.9)	923 (118.9)	12.8 (159.1)	145 (161.7)	98.9 (98.2, 99.6)
>12000	486	67.6 (119.4)	801 (128.4)	12.5 (160.4)	136 (161.5)	98.6 (97.5, 99.6)
Missing	191	72.0 (121.4)	924 (136.8)	12.3 (145.3)	147 (158.6)	98.4 (96.7, 100.0)
Fever at baseline						
No	1166	71.9 (113.4)	888 (123.9)	12.9 (154.5)	146 (159.2)	99.1 (98.5, 99.6)
Yes	343	72.1 (121.8)	859 (130.3)	12.2 (165.7)	134 (167.4)	98.3 (96.9, 99.6)
Missing	44	75.1 (117.3)	929 (118.4)	11.8 (180.9)	132 (164.7)	93.2 (85.7, 100.0)
Age (years)						
18 to 65	1192	70.0 (113.5)	800 (122.7)	12.5 (167.1)	131 (166.8)	98.4 (97.7, 99.1)
>65 to 75	284	77.1 (109.4)	997 (107.6)	13.2 (119.0)	156 (118.4)	99.6 (99.0, 100.0)
>75 to 89	288	76.8 (120.5)	1102 (120.6)	14.0 (169.6)	180 (164.7)	98.6 (97.3, 100.0)
Concomitant use of OAT1/OAT3 inhibitor(s)						
No	1631	71.7 (115.2)	869 (124.4)	12.8 (160.5)	142 (162.3)	98.6 (98.0, 99.2)
Yes	133	78.5 (103.5)	934 (114.7)	13.7 (165.4)	150 (158.5)	99.2 (97.8, 100.0)
Obesity						

Normal	1441	73.0 (115.5)	878 (124.2)	13.0 (160.2)	144 (161.4)	98.7 (98.1, 99.3)
Obesity I (29.9 ≤ BMI <34.9 kg/m^2)	208	67.9 (111.8)	841 (125.2)	12.0 (178.4)	136 (179.1)	97.6 (95.5, 99.7)
Obesity II (34.9 ≤ BMI <39.9 kg/m^2)	74	73.7 (109.6)	894 (115.2)	13.2 (139.7)	141 (140.0)	100.0 (NA)
Obesity III (BMI ≥39.9 kg/m^2)	32	64.2 (93.6)	806 (119.4)	9.7 (116.9)	115 (128.5)	100.0 (NA)
Missing	9	70.9 (87.0)	959 (106.5)	14.2 (83.4)	172 (112.8)	100.0 (NA)
Race						
Caucasian/Other	1209	68.6 (112.9)	848 (125.0)	12 (159.4)	135 (161.3)	98.3 (97.6, 99.1)
Asian (non-Chinese; non-Japanese)	248	82.2 (118.4)	968 (121.9)	14.9 (166.5)	166 (170.8)	99.6 (98.8, 100.0)
Chinese and Taiwanese	262	77.6 (112.5)	884 (120.5)	14.7 (154.9)	151 (155.1)	98.9 (97.6, 100.0)
Japanese	45	90.4 (82.6)	1021 (94.8)	16.1 (134.3)	164 (130.9)	100.0 (NA)
Asian population						
China (only)	251	78.4 (111.2)	892 (119.6)	14.9 (155.6)	153 (155.8)	98.8 (97.5, 100.0)
Japan	45	90.4 (82.6)	1021 (94.8)	16.1 (134.3)	164 (130.9)	100.0 (NA)
Korea	77	79.9 (97.2)	952 (106.5)	13.0 (135.9)	144 (138.1)	98.7 (96.2, 100.0)
Taiwan	12	59.4 (130.1)	728 (130.3)	10.2 (109.9)	115 (121.5)	100.0 (NA)
Vietnam	45	78.6 (109.1)	852 (105.2)	14.6 (116.5)	146 (119.9)	100.0 (NA)
Day 3 CrCL, mL/min (simulated ceftazidime-avibactam treatment regimen)[¶]						
8 to 15 (750/187.5 mg q24h)	4	34.3 (173.3)	551 (121.9)	6.3 (305.6)	86.3 (220.6)	7**5.0 (32.6,** 100.0)
>15 to 30 (750/187.5 mg q12h)	20	50.4 (139.5)	789 (116.5)	10.9 (174.1)	155 (143.6)	100.0 (NA)

>30 to 50 (1000-250 mg q8h)	128	58.8 (120.5)	938 (122.9)	10.2 (147.6)	148 (153.3)	98.4 (96.3, 100.0)
>50 to 80 (2000-500 mg q8h)	418	90.0 (108.0)	1213 (110.4)	15.3 (142.9)	186 (144.5)	99.0 (98.1, 100.0)
>80 to 150 (2000-500 mg q8h)	955	72.9 (105.9)	828 (112.4)	13.2 (165.5)	138 (163.4)	99.0 (98.3, 99.6)
>150 to 180 (2000-500 mg q8h)	123	58.5 (93.0)	652 (112.8)	9.9 (124.5)	103 (137.5)	98.4 (96.1, 100.0)
>180 to 610 (2000-500 mg q8h)	116	51.2 (109.6)	542 (108.1)	9.9 (171.6)	96 (155.9)	95.7 (92.0, 99.4)

[†]The joint PK/PD target was defined as 50% *f*T> 8 mg/L for ceftazidime and 50% *f*T>1 mg/L for avibactam; [‡]APACHE II scores were collected for cIAI and NP patients only, hence these data were not available for the 648 cUTI patients; data were missing for 1 cIAI patient; [¶]subjects with CrCL <50 ml/min were assumed to receive the labelled dosage regimen appropriate to their level of renal insufficiency.

APACHE II, Acute Physiology and Chronic Health Evaluation II; $AUC_{ss,0–24}$ area under the plasma concentration versus time curve at steady state BMI, body mass index; CI, confidence interval; cIAI, complicated intra-abdominal infections; $C_{max,ss}$ maximum plasma concentration at steady state; CrCL, creatinine clearance; cUTI complicated urinary tract infections; non-VAP, not ventilator-associated pneumonia; CV, coefficient of variation; NA, not applicable; NP, nosocomial pneumonia; OAT1/OAT3, organic anion transporter 1/ organic anion transporter 3; PK pharmacokinetic; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; SIRS, systemic inflammatory response syndrome; VAP, ventilator-associated pneumonia; WBC, white blood cell.

Table 4. Steady-state exposure for ceftazidime and avibactam and probability of joint PK/PD target attainment in simulated patients by indication and renal function category

Renal function category (CrCL); ceftazidime-avibactam dosing regimen[†]	Patient population	Avibactam		Ceftazidime		Joint PTA, %[‡]
		$C_{max,ss}$ geometric mean (CV), mg/L	$AUC_{ss,0-24}$ geometric mean (CV), m·h/L	$C_{max,ss}$ geometric mean (CV), mg/L	$AUC_{ss,0-24}$ geometric mean (CV), m·h/L	
Normal (>80 mL/min); 2000-500 mg q8h	cIAI	61.1 (44)	683 (45)	11.5 (83)	121 (72)	94.9
	cUTI	73 (47)	880 (49)	11.2 (87)	126 (82)	95.2
	NP	65.4 (53)	805 (55)	12.8 (94)	147 (89)	98.3
	NPv	56.8 (51)	723 (56)	11.2 (82)	131 (75)	97.2
	VAP	55.1 (59)	719 (64)	10.7 (85)	129 (79)	96.1
	Non-VAP	75.7 (43)	894 (48)	14.7 (92)	164 (93)	100.0
Mild impairment (51 to <80 mL/min); 2000-500 mg q8h	cIAI	79.6 (44)	1080 (45)	14.3 (84)	172 (71)	99.0
	cUTI	94.5 (48)	1330 (49)	13.6 (88)	172 (82)	98.7
	NP	86 (53)	1260 (55)	16 (95)	211 (87)	98.9
	NPv	76 (52)	1160 (56)	14.2 (82)	193 (73)	98.4
	VAP	74.8 (60)	1160 (62)	13.9 (88)	193 (78)	97.6
	Non-VAP	97.1 (44)	1370 (48)	17.7 (93)	226 (92)	100.0
Moderate impairment (31 to <50 mL/min); 1000-250 mg q8h	cIAI	54.2 (45)	871 (45)	9.82 (86)	143 (72)	99.3
	cUTI	65.5 (49)	1070 (49)	9.49 (90)	142 (83)	99.1
	NP	59.7 (54)	1020 (55)	11.1 (97)	175 (88)	98.8
	NPv	53.4 (54)	940 (56)	9.97 (84)	161 (74)	98.3
	VAP	52.8 (62)	941 (62)	9.77 (90)	160 (78)	97.7
	Non-VAP	66.7 (45)	1110 (48)	12.3 (96)	189 (92)	100.0

Severe 1 impairment (16 to <30 mL/min); 750-187.5 mg q12h	cIAI	47.6 (46)	768 (47)	8.88 (92)	130 (73)	99.0
	cUTI	57.8 (52)	947 (51)	8.61 (96)	129 (84)	98.6
	NP	52.3 (56)	903 (56)	10 (101)	159 (88)	98.8
	NPv	46.8 (56)	829 (57)	8.96 (88)	146 (75)	97.9
	VAP	46.4 (65)	830 (64)	8.81 (95)	145 (79)	97.3
	Non-VAP	58.4 (46)	982 (50)	11 (100)	171 (93)	100
Severe 2 impairment (6 to <15 mL/min); 750-187.5 mg q24h	cIAI	53.7 (49)	860 (50)	10.4 (100)	151 (76)	99.3
	cUTI	65.5 (56)	1060 (55)	10.1 (104)	150 (89)	98.8
	NP	59.1 (59)	1010 (60)	11.7 (109)	186 (92)	99.2
	NPv	52.6 (61)	924 (62)	10.4 (94)	169 (79)	98.7
	VAP	52.3 (70)	929 (68)	10.3 (102)	170 (84)	98.0
	Non-VAP	65.5 (48)	1090 (55)	12.8 (107)	198 (98)	100.0
ESRD; 750-187.5 mg q48h	cIAI	9.7 (105)	127 (70)	85 (59)	1570 (65)	99.6
	cUTI	9.3 (107)	127 (80)	105 (66)	1940 (70)	99.5
	NP	10.7 (113)	157 (85)	96.1 (70)	1860 (74)	99.5
	NPv	9.5 (95)	143 (71)	87.2 (72)	1720 (75)	99.1
	VAP	9.3 (103)	143 (76)	86.2 (81)	1700 (81)	98.8
	Non-VAP	11.8 (108)	168 (90)	106 (60)	2040 (69)	100.0

[†]Labelled dose adjustments for patients with renal insufficiency; [‡]joint PK/PD target was defined as 50% *f*T> 8 mg/L for ceftazidime and 50% *f*T>1 mg/L for avibactam.

$AUC_{ss,0-24}$, area under the plasma concentration versus time curve at steady state; cIAI, complicated intra-abdominal infection; $C_{max,ss}$, maximum plasma concentration at steady state; cUTI, complicated urinary tract infection; CV, coefficient of variation; ESRD, end-stage renal disease; non-VAP, not ventilator-associated pneumonia; NP, nosocomial pneumonia; NPv, nosocomial pneumonia with ventilator in the hospital room on the day of pharmacokinetic sampling, which includes ventilator-associated pneumonia and hospital-acquired pneumonia in patients who were receiving ventilation on the day of sampling; PTA, probability of target attainment; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; q48h, every 48 hours; VAP, ventilator-associated pneumonia.