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Original Article

Population pharmacokinetics of tazobactam/ceftolozane in Japanese patients with complicated urinary tract infection and complicated intra-abdominal infection☆

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ABSTRACT

Tazobactam/ceftolozane is a combination of a β-lactamase inhibitor and a cephalosporin antibiotic, with recommended dosage for patients with normal renal function of tazobactam 0.5 g/ceftolozane 1 g administered as a 1-h intravenous infusion every 8 h. The doses in patients with moderate and severe renal impairment are recommended to be reduced by half and 1/4th, respectively. The dose in patients undergoing dialysis is a single loading dose of 750 mg followed after 8 h by a 150 mg maintenance dose. In order to evaluate pharmacokinetics (PK) in Japanese patients, individual Bayes PK parameters were derived using the previously developed population PK models. Furthermore, attainment of PK/pharmacodynamic target in Japanese patients was calculated to confirm the recommended dosage.

Based on PK data from 200 Japanese patients in the phase 3 studies, including patients with mild and moderate renal impairment, individual tazobactam/ceftolozane PK parameters were derived. No clinically relevant difference was observed in tazobactam/ceftolozane exposures between Japanese and non-Japanese patients. All Japanese patients achieved a target percent of time that free ceftolozane concentrations are above the minimum inhibitory concentration (MIC) of 30% for MICs of up to 8 μg/mL. Also for tazobactam, all Japanese patients achieved a target percent of time that the free tazobactam concentration exceeds a threshold concentration (1 μg/mL) of 20%. The results suggest that the doses will be efficacious in the Japanese population.

The results indicate that the recommended dose in patients with normal renal function or renal impairment is appropriate in Japanese patients.

1. Introduction

Tazobactam/ceftolozane (TAZ/CTLZ) is a combination of a β-lactamase inhibitor, TAZ, and a cephalosporin antibiotic, CTLZ, and is developed for treatment of serious bacterial infections. TAZ/CTLZ is administered as intravenous (IV) infusion. CTLZ inhibits penicillin binding proteins essential for bacterial growth and, as a result, produces an antibacterial effect. TAZ prevents CTLZ from hydrolysis by inhibiting β-lactamase enzymes responsible for drug resistance and broadens CTLZ coverage to include the most common extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* [1–4].

The pharmacokinetics (PK) of both single- or multiple-dose IV infusions of TAZ/CTLZ was dose proportional and linear up to 1 g/2 g as a single dose. CTLZ is primarily eliminated as the parent drug from the systemic circulation into the urine by glomerular filtration, whereas TAZ is mostly eliminated into the urine as the parent drug but with a small fraction of dose converted by the liver to a microbiologically inactive M1 metabolite [5–7].

Like other β-lactam antibiotics, the PK/pharmacodynamic (PD) parameter that most closely correlates with CTLZ efficacy is the time, as a percent of the dosing interval, that the free drug concentration of CTLZ are above the minimum inhibitory concentration (MIC) of the infecting organism (%fT > MIC) [8].

☆ All authors meet the ICMJE authorship criteria.

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TAZ/CTLZ is approved in the United States, Canada, and other regions of the world for the treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) in adults. The totality of the data in the clinical development program supports a recommended dose in patients with normal renal function or mild renal impairment, defined as creatinine clearance (CLcr > 50 mL/min), of 1.5 g dose (0.5 g TAZ and 1 g CTLZ) administered as a 1-h IV infusion every 8 h based on the totality of the data in the non-Japanese clinical development. The doses in patients with moderate (CLcr 30–50 mL/min) and severe (CLcr 15–29 mL/min) renal impairment are recommended to be reduced by half (i.e. 750 mg TAZ/CTLZ every 8 h) and 1/4th (i.e. 375 mg TAZ/CTLZ every 8 h), respectively. The dose in patients with end-stage renal disease (ESRD) on hemodialysis is a single loading dose of 750 mg TAZ/CTLZ followed after 8 h by a 150 mg maintenance dose administered every 8 h. For patients with changing renal function, CLcr is monitored at least daily and the dose adjustment is recommended [9]. These dose adjustments are recommended based on data of clinical pharmacology studies.

One phase 1 study in healthy Japanese and non-Japanese subjects was conducted to characterize the PK of TAZ/CTLZ following single 1.5 g and 3 g doses as a 1-h IV infusion, suggesting that the PK of TAZ/CTLZ is dose proportional and similar between healthy Japanese and non-Japanese subjects, and the cumulative amount of CTLZ and TAZ excreted in urine was similar between the ethnic groups [10].

In Japan, two phase 3 studies in Japanese patients with cUTI and cIAI were conducted to confirm the safety and efficacy of TAZ/CTLZ in Japanese patients and for an approval application in Japan [11,12]. Furthermore, although there was no PK data that the dose was adjusted based on CLcr during the phase 3 studies in non-Japanese patients, the two phase 3 studies included Japanese patients with moderate renal impairment, and CTLZ and TAZ PK after dose adjustment based on CLcr during these studies in these patients with cUTI and cIAI were confirmed for the first time.

The objectives of this paper were to:

- Derive individual empirical Bayes parameters and estimate the CTLZ and TAZ exposures at steady state (area under the plasma concentration–time curve at steady state [AUCss] and maximum concentration [Cmax, which is equivalent to concentration at the end of infusion]) in Japanese cUTI and cIAI patients in the phase 3 studies using the population PK models
- Summarize PK parameters in the Japanese population and compare with those in non-Japanese adults for whom efficacy and safety has been previously established
- Calculate PK/PD target attainments in Japanese patients to support dose recommendation in Japan
- Evaluate the appropriateness of dose adjustment in Japanese patients with moderate renal impairment

2. Patients and methods

2.1. Study design and target population

Two multicenter, open-label, noncomparative phase 3 studies in Japanese patients with cUTI (MK-7625A-014, ClinicalTrials.gov Identifier: NCT02728089) [11] and cIAI (MK-7625A-013, ClinicalTrials.gov Identifier: NCT02739997) [12] were conducted. Patients received TAZ/CTLZ 1.5 g (TAZ 0.5 g/CTLZ 1 g) intravenously every 8 h for 1-h for 7 days (for cUTI) and for 4–14 days (for cIAI). Patients with CLcr of 30–50 mL/min received TAZ/CTLZ 750 mg (TAZ 250 mg/CTLZ 500 mg) for the same treatment period. CLcr was estimated by the Cockcroft-Gault equation [13]. The criteria of diagnose cUTI and cIAI with patients were used the same criteria used in the paper of Arakawa et al. [11] and Mikamo et al. [12], respectively. For the empirical Bayes analysis, CTLZ and TAZ plasma concentration data from these phase 3 studies in Japanese patients were used. These studies provided PK data from 100 and 115 subjects, respectively, with samples collected at pre-dose on Day 1, and at pre-dose, end of infusion, and 0.5–1.5 h, 2.5–3.5 h and 5.5–7 h after the end of infusion on Day 3, 4 or 5. Relevant subject demographics (age, body mass index [BMI], weight, sex, CLcr, and estimated glomerular filtration rate [eGFR] [14]) were collected. For the empirical Bayes analysis, weight and eGFR were used as covariates.

2.2. Bioanalysis

Plasma concentrations of CTLZ and TAZ were quantified with liquid chromatography with tandem mass spectrometry (LC/MS/MS) method that was developed and validated in accordance with regulatory guidance [15]. The assay lower limits of quantitation of CTLZ and TAZ were 0.250 μg/mL and 0.100 μg/mL, respectively.

2.3. Population PK models

The present analysis has been conducted based on the existing population PK models for CTLZ and TAZ [16]. Two-compartment models with first-order elimination and moderate between-subject variability well described the concentration–time profiles of CTLZ and TAZ in adult patients and healthy subjects as well as pediatric patients following infusions of 1 h with doses ranging from 250 to 3000 mg for CTLZ and from 250 to 1500 mg for TAZ administered as multiple doses either every 6 h, every 8 h, every 12 h, or daily. The CTLZ and TAZ population PK parameter estimates are shown in Appendix 1 and 2, respectively.

The parameters in the models described above were not re-estimated with the TAZ and CTLZ concentration data from Japanese cIAI/cUTI patients in the phase 3 studies. Rather, individual empirical Bayes estimates for Japanese patients were obtained using the models based on demographic data (body weight, eGFR and infection status) and TAZ/CTLZ concentrations. The adequacy of this approach was evaluated based on the following diagnostic plots:

Table 1
Number of patients and observations in the analysis dataset (MK-7625A-013 and MK-7625A-014).

Analyte	Study	Disease	N of patients	[%] of patients	N of PK observations	[%] of PK observations
Ceftolozane	013	cIAI	97	48.5	419	46.9
	014	cUTI	103	51.5	474	53.1
	Total		200	100	893	100
Tazobactam	013	cIAI	97	48.5	373	46.2
	014	cUTI	103	51.5	435	53.8
	Total		200	100	808	100

Abbreviation: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection.

- Prediction-corrected observed concentrations in Japanese patients from MK-7625A-013 and MK-7625A-014 compared with predicted concentration range from the population PK models. Observed and simulated concentrations were corrected based on the typical population prediction. Simulated concentrations were generated using 1000 simulations from the population PK models.
- Observed data versus individual predicted data (DV vs IPRED) with a line of unity and a locally weighted scatterplot smoothing (LOESS) line
- Time after first dose versus individual weighted residuals (Time vs |IWRES|) and a LOESS line

2.4. Calculation of model-derived PK parameters

Individual Bayes PK parameters (i.e. individual CL, intercompartmental clearance [Q], central volume of distribution [Vc] and peripheral volume of distribution [Vp]) in Japanese and non-Japanese patients were estimated using the above population PK models [16] based on demographic data and TAZ/CTLZ concentrations.

The following PK parameters were derived from these individual Bayes PK parameters and actual dosing information on the day for the last PK sampling (Day 3, 4 or 5): AUCss, Cmax and terminal elimination half-life (t1/2).

Descriptive statistics of PK parameters (AUCss, Cmax and t1/2) and empirical Bayes estimates (CL and volume of distribution at steady state [Vss]) were summarized for all patients (Japanese and non-Japanese). Vss was calculated as the sum of Vc and Vp. The following statistics were presented: number of observations, geometric mean, and percent geometric coefficient of variation (%GCV).

2.5. Calculation of PK/PD target attainments in Japanese patients

Individual concentration–time profiles for CTLZ and TAZ were simulated after the first dose with 5-min intervals between time points based on Bayes PK parameters (i.e. individual CL, Q, Vc and Vp) and actual dosing regimens for each patient. The first dose simulated profile was used to calculate target attainment as it is important for antibacterials to meet their PK/PD driver of efficacy after first dose.

Table 2
Summary of demographic characteristics in the Japanese analysis dataset (MK-7625A-013 and MK-7625A-014).

Subject Characteristic	Mean	SD	Median	Min	Max	N
Baseline age (years)	64.7	15.7	68	20	90	200
Baseline BMI (kg/m^2)	23.9	4.55	23.5	14.9	42.6	199[a]
Baseline eGFR (mL/min/1.73 m^2)	74.7	25.1	73.7	26.3	209	200
Baseline CLcr (mL/min)	82.3	33.1	75.2	30.1	223	200
Baseline weight (kg)	61.1	13.9	59.4	33.5	110	200
Sex (male/female)	N = 98/102; [%] = 49/51					200

Abbreviation: BMI, body mass index; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; Max, maximum; Min, minimum; SD, standard deviation.
[a] One patient had missing height information.

2.5.1. CTLZ target attainment

The PK target that best correlates with *in vivo* efficacy of CTLZ is the percent of time that free plasma concentrations of CTLZ are above a minimum inhibitory concentration (%*f*T > MIC). Since data from a neutropenic mouse thigh infection model showed that the %T > MIC ranged from 26.7% to 35.3% for a 1-log kill with dosing of CTLZ against four wild-type *Enterobacteriaceae* and four *Pseudomonas aeruginosa* strains [8], a %*f*T > MIC of 30% was used as a target value for the efficacy. Concentrations from the simulated profiles after the first dose were adjusted for protein binding (21% for CTLZ). The simulated free concentration–time profiles were used to calculate %*f*T > MIC and the percentage of subjects attaining %*f*T > MIC of at least 30% was calculated. This was calculated for various MICs (<0.06, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64 and 128 μg/

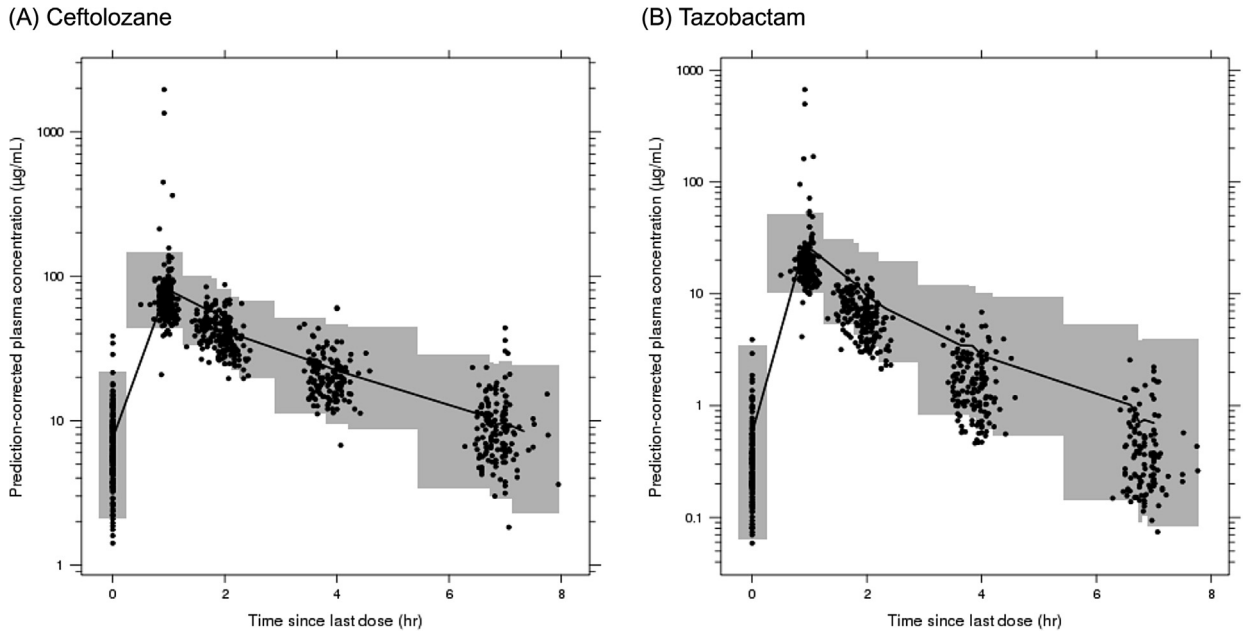

Fig. 1. Prediction-corrected observed (A) ceftolozane and (B) tazobactam concentrations at steady state (day 3, 4 or 5) in Japanese patients from MK-7625A-013 and MK-7625A-014 compared with predicted concentrations range from the population PK model (semi-log scales). Closed circle represents Japanese individual prediction-corrected plasma concentration; solid line is median prediction from the model and the shaded area represents the 90% prediction interval.

mL) that encompassed the MIC distribution observed in MK-7625A-013 and MK-7625A-014.

2.5.2. TAZ target attainment

Since TAZ does not have intrinsic antibacterial activity, an MIC cannot be determined. Instead, the threshold drug concentration (Ct) needed to effectively neutralize the β-lactamase enzyme produced by bacteria was used for target attainment. In this report, the time above a Ct of 1 μg/mL for free TAZ exposures of 20% was used, which is supported by data from a mouse model and clinical studies [8,17,18]. Concentrations from the simulated profiles after the first dose were adjusted for protein binding (30% for TAZ). The simulated free concentration–time profiles were used to calculate the percent of time that free TAZ plasma concentration was above a threshold concentration (%*f*T > Ct) and the pecentage of subjects attaining %*f*T > CT of at least 20% was calculated.

2.6. Software

Individual Bayes PK parameters (i.e. individual CL, Q, Vc and Vp) for Japanese patients were obtained based on the previously estimated model parameter values and the TAZ/CTLZ plasma concentrations in Japanese patients in the phase 3 studies using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, Maryland

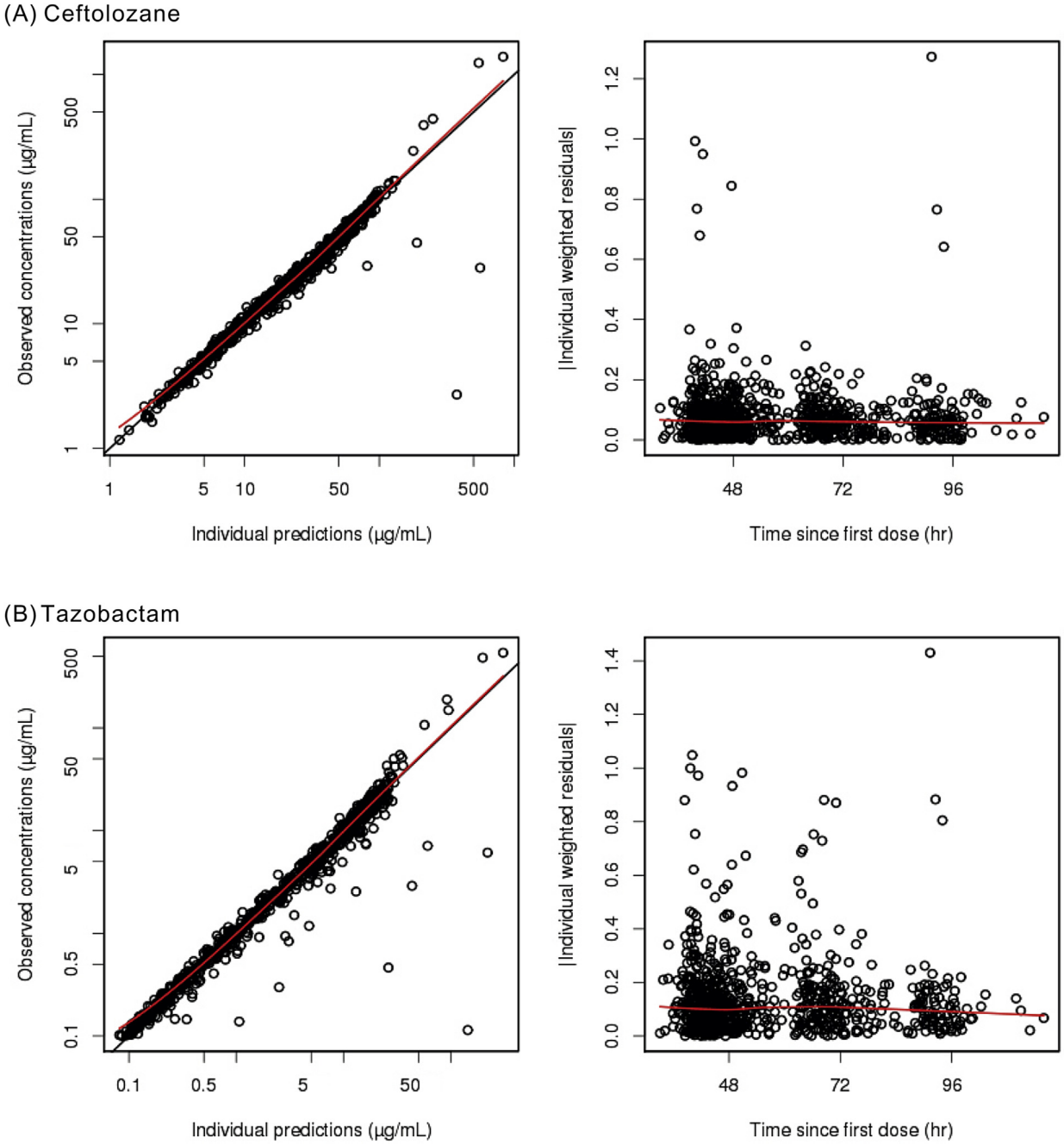

Fig. 2. Goodness of fit plots of (A) ceftolozane and (B) tazobactam in Japanese patients. Black lines are lines of identity; red lines are the smooth lines.

Table 3
Summary statistics of ceftolozane and tazobactam PK parameters at steady state in Japanese patients with CLcr >50 mL/min (1.5 g) and CLcr 30–50 mL/min (750 mg) receiving an intravenous 1-h Infusion of tazobactam/ceftolozane every 8 h.

Analyte	Ceftolozane				Tazobactam			
CLcr	>50 mL/min (N = 184)		30–50 mL/min (N = 16)		>50 mL/min (N = 184)		30–50 mL/min (N = 16)	
Dose	1000 mg		500 mg		500 mg		250 mg	
PK Parameters	GM	%GCV	GM	%GCV	GM	%GCV	GM	%GCV
CL (L/h)	5.04	43.5	2.72	27.7	15.5	57.9	8.65	26.7
Vss (L)	15.3	37.7	13.1	23.5	19.9	39.8	16.0	26.2
t1/2 (h)	2.46	27.3	3.59	19.3	1.32	27.2	1.62	14.4
Cmax (μg/mL)	69.7[a]	40.6	49.9	28.6	18.7[a]	45.7	13.8	26.5
AUCss (μg h/mL)	198[a]	43.7	184	27.7	32.1[a]	57.8	28.9	26.7

Note: As per protocol, the dose was adjusted from 1.5 g to 750 mg for subjects with CLcr 30–50 mL/min. Patients were stratified by the CLcr that was observed in each patient before PK sample was taken. Vss was calculated as the sum of the volume of the central compartment (Vc) and volume of the peripheral compartment (Vp).
Abbreviation: AUCss, area under the concentration time curve at steady state; CL, clearance; CLcr, creatinine clearance; Cmax, maximum concentration; %GCV, percent geometric coefficient of variation; GM, geometric mean; t1/2, terminal elimination half-life; Vss, volume of distribution at steady state.
[a] N = 183, 1 patient with dose of 1.316 g due to dosing error was excluded from the summary statistics of AUCss and Cmax.

Table 4
Summary of ceftolozane and tazobactam PK parameter values at steady state in Japanese and non-Japanese patients with CLcr >50 mL/min following intravenous infusion of 1.5 g ceftolozane/tazobactam every 8 h.

Analyte	Ceftolozane				Tazobactam			
Study group	Japanese (N = 184)		non-Japanese (N = 150)		Japanese (N = 184)		non-Japanese (N = 77)	
PK parameters	GM	%GCV	GM	%GCV	GM	%GCV	GM	%GCV
CL (L/h)	5.04	43.5	5.64	53.1	15.5	57.9	12.3	121
Vss (L)	15.3	37.7	19.0	44.9	19.9	39.8	20.7	45.8
t1/2 (h)	2.46	27.3	2.74	42.1	1.32	27.2	1.69	55.1
Cmax (μg/mL)	69.7[a]	40.6	59.8	46.6	18.7[a]	45.7	21.5	79.0
AUCss (μg h/mL)	198[a]	43.7	177	53.1	32.1[a]	57.8	40.7	121

Note: Patients were stratified by the CLcr that was observed in each patient before PK sample was taken. Vss was calculated as the sum of the volume of the central compartment (Vc) and volume of the peripheral compartment (Vp).
Abbreviation: AUCss, area under the concentration time curve at steady state; CL, clearance; CLcr, creatinine clearance; Cmax, maximum concentration; %GCV, percent geometric coefficient of variation; GM, geometric mean; t1/2, terminal elimination half-life; Vss, volume of distribution at steady state.
[a] N = 183, 1 patient with dose of 1.316 g due to dosing error was excluded from the summary statistics of AUCss and Cmax.

USA) with the first order conditional estimation method with interaction (FOCE-I). Exploratory plots and final figures were generated using PsN (psn.sourceforge.net) and R (R-project, www.r-project.org, version 3.2.4). Non-compartment analysis was conducted using Phoenix™ WinNonlin® (version 6.3.0.395). R was also used to calculate the PK/PD target attainments.

3. Results

3.1. Summary of patients and samples included in the analysis

The final analysis dataset from studies MK-7625A-013 and MK-7625A-014 comprised of 893 CTLZ concentrations and 808 TAZ concentrations from 200 Japanese patients. The number of Japanese patients with cUTI and cIAI and PK observations in the final analysis datasets is provided in Table 1. There were 97 patients with cIAI and 103 patients with cUTI.

3.2. Summary of demographic characteristics included in the analysis

Table 2 summarize descriptive statistics of demographic characteristics included in the analysis for Japanese patients. The Japanese patients were aged 20–90 years, weighed 33.5–110 kg, and had baseline CLcr values ranging from 30.1 to 223 mL/min. One patient had missing baseline BMI value. The numbers of males were

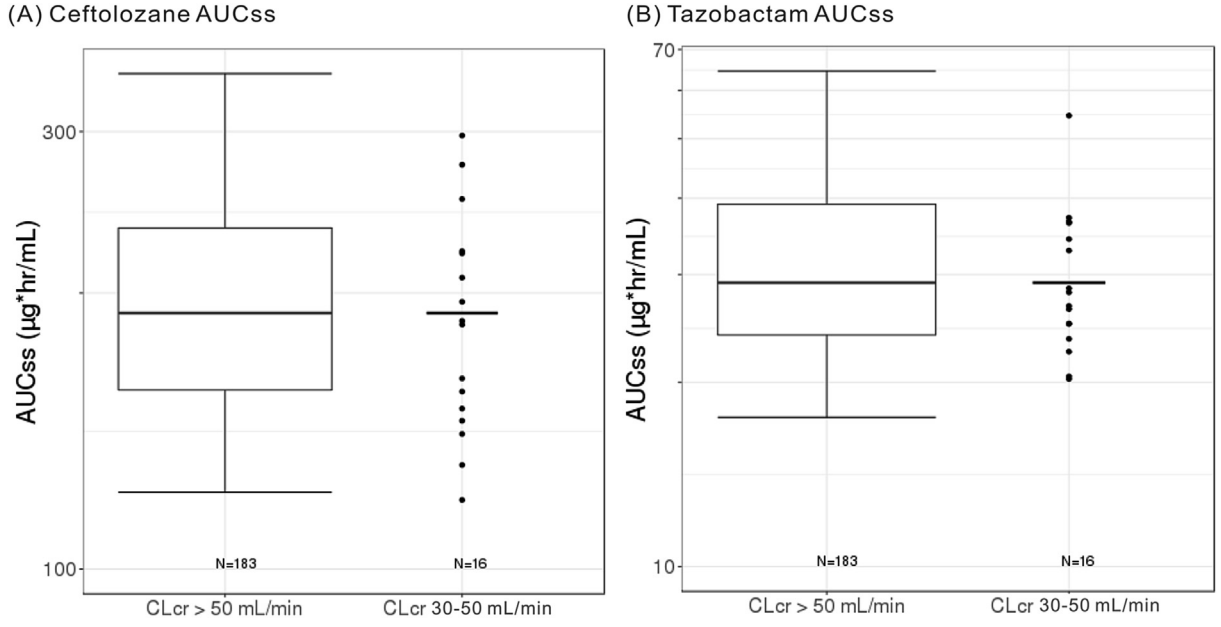

Fig. 3. Comparison of ceftolozane and tazobactam AUCss between Japanese with CLcr >50 mL/min and 30–50 mL/min following intravenous infusion of 1.5 g or 750 mg ceftolozane/tazobactam every 8 h (log scales). Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles; bars are medians. One Japanese patient with dose of 1.316 g due to dosing error was excluded. Abbreviation: AUCss, area under the concentration time curve at steady state; CLcr, creatinine clearance.

similar to that of females (49% and 51% were male and female, respectively).

3.3. Pharmacokinetic model application

Fig. 1 presents the CTLZ and TAZ plasma prediction-corrected concentrations for the Japanese patients, together with a predicted concentration range (median and 90% prediction interval) from the population PK models. The prediction-corrected observed concentrations in Japanese generally fall within the range of predicted concentrations, indicating that the population PK models provide an adequately described the CTLZ and TAZ plasma concentrations in Japanese patients. Individual predicted concentrations in Japanese patients were evaluated based on the diagnostic plots. As shown in Fig. 2, the goodness of fit plots demonstrated the absence of systematic bias as a function of drug concentration although the large difference between predicted and observed concentrations was observed in some patients who had high concentrations at the end of infusion.

3.4. Calculation of model-derived PK parameters

3.4.1. Calculation of model-derived PK parameters in Japanese patients

The CTLZ and TAZ PK parameters at steady state in Japanese patients with cUTI and cIAI receiving an IV 1-h infusion of TAZ/CTLZ 1.5 g or 750 mg every 8 h are presented in Table 3. In Japanese cUTI and cIAI, dose adjustments were made in patients with CLcr 30–50 mL/min and therefore the results are summarized stratified by CLcr that was observed in each patient before PK sample was taken.

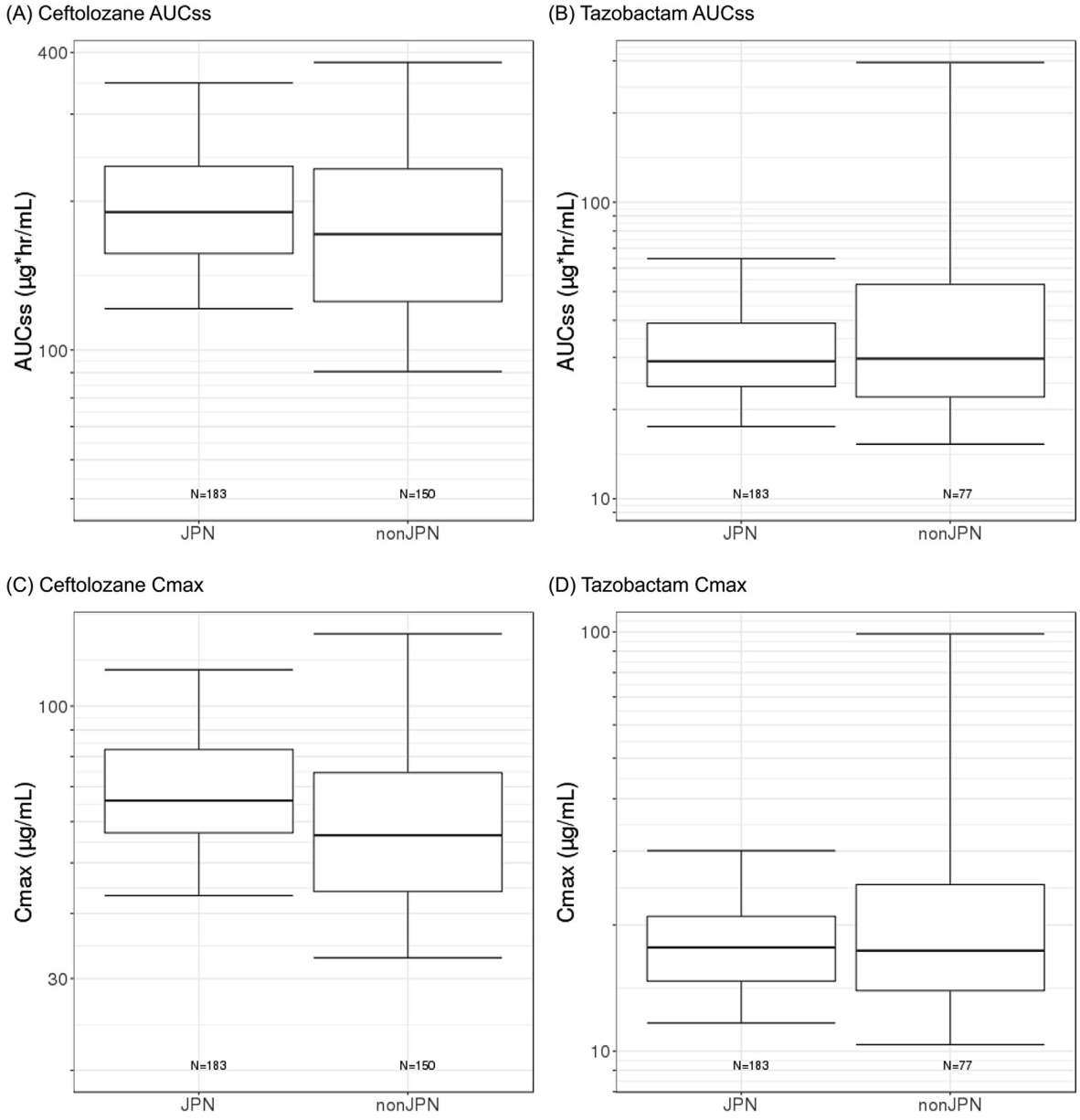

Fig. 4. Comparison of ceftolozane and tazobactam PK parameter values between Japanese and non-Japanese patients with CLcr >50 mL/min following intravenous infusion of 1.5 g ceftolozane/tazobactam every 8 h (log scales). Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. One Japanese patient with dose of 1.316 g due to dosing error was excluded. Abbreviation: AUCss, area under the concentration time curve at steady state; CLcr, creatinine clearance; Cmax, maximum concentration.

As presented in Fig. 3, the distributions of individual AUCss of CTLZ and TAZ substantially overlapped between patients with CLcr >50 mL/min and 30–50 mL/min. A comparison of the central tendencies of the distributions indicated similarity between these patients.

3.4.2. Comparison between Japanese and non-Japanese

The CTLZ and TAZ PK parameters at steady state in Japanese and non-Japanese patients with CLcr >50 mL/min following IV 1-h infusion of TAZ/CTLZ 1.5 g every 8 h are presented in Table 4. As presented in Fig. 4, the distributions of individual PK parameter values of CTLZ and TAZ substantially overlapped and the central tendencies of the distributions were also similar between these groups. Overall, the PK parameters of CTLZ and TAZ were similar between Japanese and non-Japanese patients.

3.5. Calculation of PK target attainments in Japanese patients

In Fig. 5, the percent of subjects who attained the PK/PD target for CTLZ was plotted versus MIC values with MIC histograms of *Escherichia coli* (ESBL+ and ESBL−), *Klebsiella pneumoniae* (ESBL+ and ESBL−), *P. aeruginosa*, *Streptococcus anginosus*, and *Bacteroides fragilis* from the samples collected at baseline visit in MK-7625A-013 and MK-7625A-014. In order to evaluate target attainment in subjects who received a dose adjustment based on CLcr values, the data were stratified according to subjects with CLcr >50 mL/min and subjects with CLcr 30–50 mL/min that each subject observed at baseline. As shown in Fig. 5, 100% of patients had a CTLZ *%fT* >MIC of 30% for MICs up to 8 μg/mL in subjects with CLcr 30–50 mL/min as well as in subjects with CLcr >50 mL/min.

In Fig. 6, the percent of subjects who attained the PK/PD target for TAZ was plotted. For TAZ, 100% of patients achieved a *%fT* >Ct of 20% for a Ct of 1 μg/mL in subjects with CLcr 30–50 mL/min as well as in subjects with CLcr >50 mL/min.

4. Discussion

The analysis herein aims to generate empirical Bayes estimates for CTLZ and TAZ in Japanese cUTI and cIAI patients in two phase 3 studies, summarize PK parameters in the Japanese population and compare with those in non-Japanese adults for which efficacy and safety has been previously established, and calculate the PK/PD target attainments in Japanese patients to support dose recommendation in Japan.

Previously, the population PK models used data from 13 clinical studies, including one study in healthy Japanese subjects [16]. A full covariate analysis was performed to identify covariates such as patient demographic factors (age, body weight, sex, and race), renal function (eGFR) and infection status. Body weight, eGFR, and infection status were selected as significant covariates but race and sex were not selected. Renal function and weight were identified as significant predictors of the PK of both of CTLZ and TAZ. Renal function, as measured by eGFR, significantly affects the clearance (CL) of both CTLZ and TAZ. The influence of weight on the central CL and (central and peripheral) volume parameters of both compounds was well described by fitted allometric scaling exponents. The CL of TAZ in patients with any infection was 67.7% of the CL in healthy adults. Further, the observed concentration in Japanese patients were generally within the prediction intervals from the population PK models without re-estimating the model parameters, which indicates that the population PK models provides an adequate representation of the CTLZ and TAZ PK in Japanese patients. Therefore, it was appropriate to calculate empirical Bayes estimates (i.e. individual CL, Q, Vc and Vp) in Japanese patients using the population PK models without re-estimating the model parameters with concentration data from the phase 3 studies in Japanese patients.

The PK parameters of CTLZ and TAZ were similar between Japanese and non-Japanese patients. The distributions of individual PK parameter values of CTLZ and TAZ overlapped between

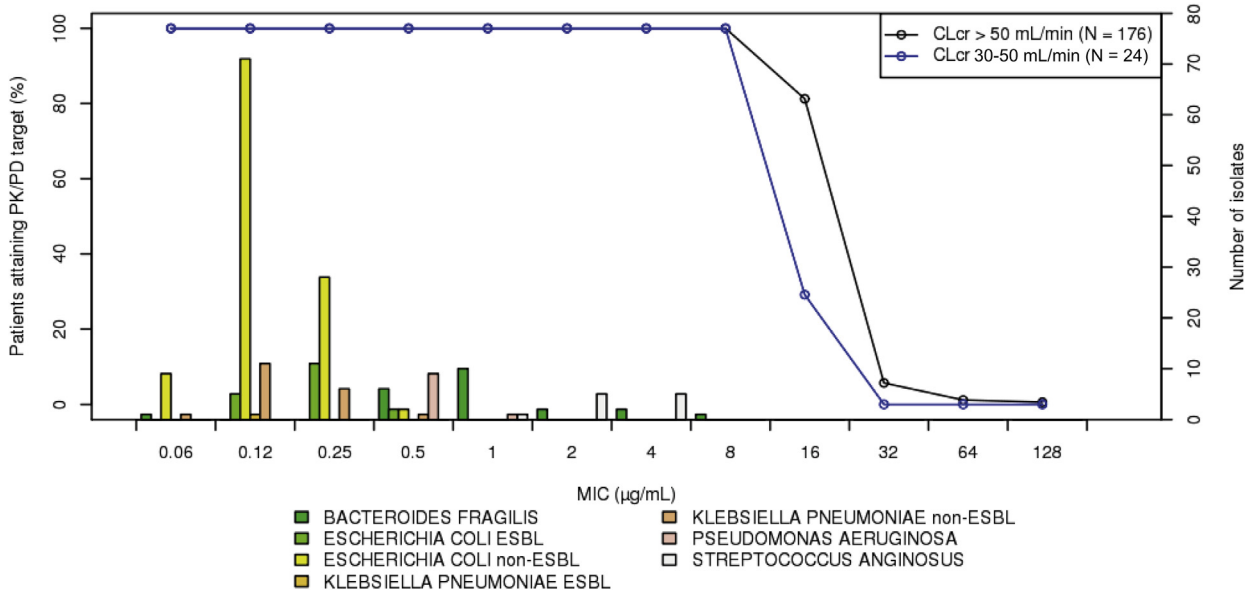

Fig. 5. Percentage of subjects achieving greater than 30% of the dosing interval above MIC for ceftolozane overlaid on MIC histograms of *Escherichia coli* (ESBL+ and ESBL−), *Klebsiella pneumoniae* (ESBL+ and ESBL−), *Pseudomonas aeruginosa*, *Streptococcus anginosus*, and *Bacteroides fragilis* from Japanese phase 3 Clinical Trials. Patients were stratified by baseline CLcr. The PK/PD target is to achieve greater than 30% of the dosing interval above MIC. Lines represent patients attaining PK/PD target (%). Bars represent number of isolates. Abbreviation: CLcr, creatinine clearance; ESBL, extended-spectrum β-lactamase; MIC, minimum inhibitory concentration; PK/PD: pharmacokinetic/pharmacodynamics.

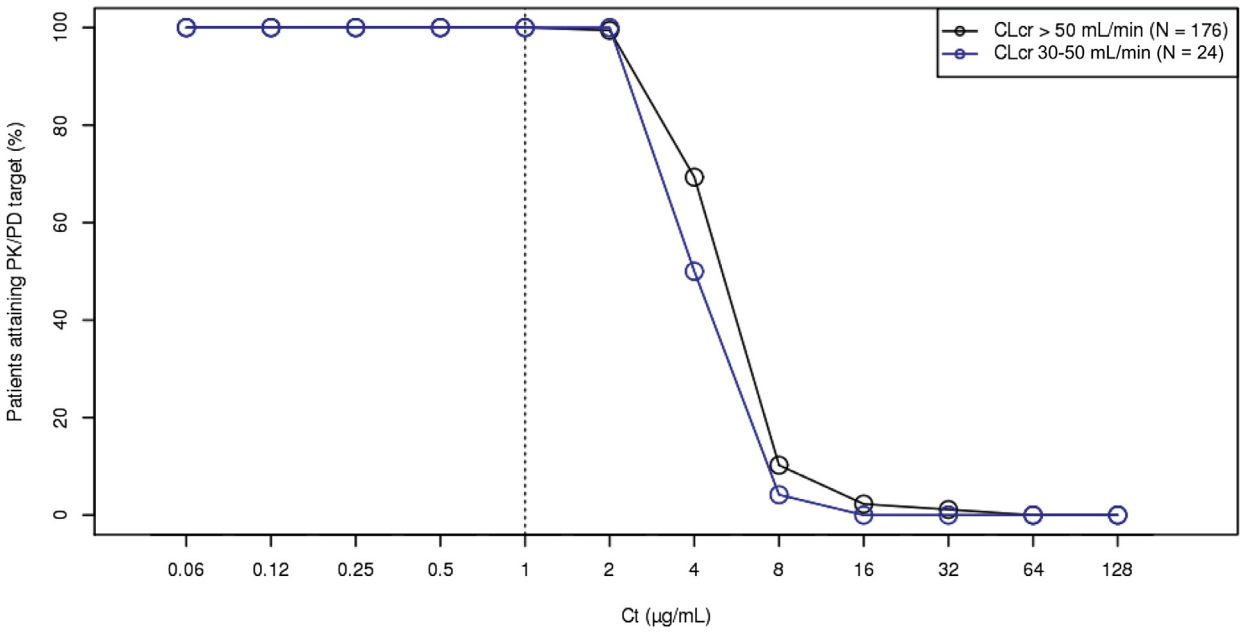

Fig. 6. Percentage of subjects achieving greater than 20% of the dosing interval above threshold concentration (Ct) for tazobactam. Patients were stratified by baseline CLcr. The PK/PD target is to achieve greater than 20% of the dosing interval above Ct. The vertical line represents a Ct of 1 μg/mL. Abbreviation: CLcr, creatinine clearance; Ct, threshold concentration; PK/PD: pharmacokinetic/pharmacodynamics.

Japanese and non-Japanese patients. The geometric mean values of AUCss for CTLZ in Japanese and non-Japanese were 198 μg h/mL and 177 μg h/mL, respectively, and the geometric mean values of Cmax were 69.7 μg/mL and 59.8 μg/mL, in Japanese and non-Japanese, respectively. For TAZ, the geometric mean values of AUCss in Japanese and non-Japanese were 32.1 μg h/mL and 40.7 μg h/mL, respectively and the geometric mean values of Cmax were 18.7 μg/mL and 21.5 μg/mL, in Japanese and non-Japanese, respectively. Furthermore, dose-normalized PK parameters for CTLZ and TAZ were similar between healthy Japanese and non-Japanese subjects [10].

CTLZ and TAZ are excreted primarily via the renal route. Based on studies conducted in non-Japanese, the CTLZ dose-normalized median AUC increased 1.4-fold, 2.5-fold, and 4.4-fold in subjects with mild (60–89 mL/min), moderate (30–59 mL/min), and severe (15–29 mL/min) renal impairment, respectively, compared to healthy subjects with normal (>90 mL/min) renal function [19]. The respective TAZ dose-normalized median AUC increased 1.2-fold, 2.2-fold, and 3.8-fold [19]. Based on these results, CTLZ and TAZ dose in non-Japanese patients with moderate or severe renal impairment is recommended to be reduced by 2-fold (i.e. 750 mg) or 4-fold (i.e. 375 mg), respectively. To maintain similar systemic exposures to those with normal renal function, dosage adjustment is required in non-Japanese patients [9].

In Japanese patients with cUTI and cIAI, dose was similarly adjusted in patients with CLcr 30–50 mL/min, whereby these subjects received a dose of 750 mg and patients with CLcr >50 mL/min received a dose of 1.5 g. After dose adjustments based on CLcr cutoffs approved in non-Japanese patients, the exposures of CTLZ and TAZ was comparable in Japanese patients with CLcr 30–50 mL/min and those with CLcr >50 mL/min, supporting appropriateness of the recommended dose adjustment in non-Japanese patients based on data of phase 3 studies in Japanese patients with moderate renal impairment.

100% of Japanese patients achieved target CTLZ %*f*T >MIC for MICs of up to 8 μg/mL and target TAZ %*f*T >Ct for a Ct of 1 μg/mL, in patients with CLcr 30–50 mL/min and CLcr >50 mL/min. The results suggest that the doses will be efficacious in the Japanese population with moderate renal insufficiency.

This analysis has a limitation. The subjects with severe renal function (CLcr < 30 mL/min), or requirement for peritoneal dialysis or oliguria at screening visit were excluded in the two Japanese phase 3 studies. Therefore, PK parameters in Japanese patients with severe renal function or ESRD on hemodialysis could not be evaluated in this analysis.

Taken together, results from this analysis indicate that the same recommended dosing regimens in Japanese and non-Japanese patients with cUTI and cIAI are appropriate.

Conflict of interest

Kajal Larson, Matthew L. Rizk and Hwa-ping Feng are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and all other authors are employees of MSD K.K. Employees may hold stock and/or stock options in the company.

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Appendix 1

Parameter estimates and standard errors from the population pharmacokinetic model for ceftolozane.

Parameter	Final parameter estimate	Interindividual variability/residual variability
	Typical value	Magnitude
CL: systemic clearance (L/h)	5.882	34.61 %CV
CL: body weight on CL (power)	0.7637	
CL: eGFR on CL (power)	0.7036	
Vc: volume of distribution for central compartment (L)	10.64	44.26 %CV
Vc: body weight on Vc (power)	1.124	
Q: intercompartmental clearance (L/h)	2.545[a]	NE
Vp: volume of distribution for peripheral compartment (L)	4.227[a]	16.33 %CV
Vp: body weight on Vp (power)	0.4840	
Cov (IIV in Vc, IIV in CL)[b]	0.07624	NA
Residual variability: proportional	0.02373	15.41 %CV
Residual variability: additive	0.008780	0.09370 SD

Abbreviations: %CV, coefficient of variation expressed as a percentage; eGFR, estimated glomerular filtration rate; IIV, interindividual variability; NA, not applicable; NE, not estimated; SD, standard deviation.
[a]The following parameter estimates were found to be highly correlated ($r^2 = 0.9313$).
[b]The calculated correlation coefficient (r) of the off-diagonal omegas was 0.4977 with $r^2 = 0.2477$ for cov (IIV in Vc, IIV in CL).

Appendix 2

Parameter estimates and standard errors from the population pharmacokinetic model for tazobactam.

Parameter	Final prameter estimate	Interindividual variability/residual variability
	Typical Value	Magnitude
CL: systemic clearance (L/h)	20.8[a]	52.9 %CV
CL: body weight on CL (power)	0.652	
CL: eGFR on CL (power)	0.733	
CL: any infection on CL (proportional)	0.677	
Vc: volume of distribution for central compartment (L)	12.9[a]	43.9 %CV[b]
Vc: body weight on Vc (power)	0.737	
Q: intercompartmental clearance (L/h)	4.06	NE
Q: body weight on Q (power)	0.75 Fixed	
Vp: volume of distribution for peripheral compartment (L)	5.06	25.9 %CV
Vp: body weight on Vp (power)	0.830	
Cov (IIV in Vc, IIV in CL)[c]	0.203[b]	NA
Residual variability: proportional	0.0555	23.6 %CV

Abbreviations: %CV, coefficient of variation expressed as a percentage; eGFR, estimated glomerular filtration rate; IIV, interindividual variability; NA, not applicable; NE, not estimated.
[a]The following parameter estimates were found to be highly correlated ($r^2 = 0.898$).
[b]The following parameter estimates were found to be highly correlated ($r^2 = 0.861$).
[c]The calculated correlation coefficient (r) of the off-diagonal omegas was 0.875 with ($r^2 = 0.766$) for cov (IIV in Vc, IIV in CL).

References

[1] Titelman E, Karlsson IM, Ge Y, Giske CG. In vitro activity of CXA-101 plus tazobactam (CXA-201) against CTX-M-14- and CTX-M-15-producing *Escherichia coli* and *Klebsiella pneumoniae*. Diagn Microbiol Infect Dis 2011;70:137–41. https://doi.org/10.1016/j.diagmicrobio.2011.02.004.

[2] Zhanel GG, Chung P, Adam H, Zelenitsky S, Denisuik A, Schweizer F, et al. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. Drugs 2014;74:31–51. https://doi.org/10.1007/s40265-013-0168-2.

[3] Farrell DJ, Sader HS, Flamm RK, Jones RN. Ceftolozane/tazobactam activity tested against Gram-negative bacterial isolates from hospitalised patients with pneumonia in US and European medical centres (2012). Int J Antimicrob Agents 2014;43:533–9. https://doi.org/10.1016/j.ijantimicag.2014.01.032.

[4] Sader HS, Farrell DJ, Castanheira M, Flamm RK, Jones RN. Antimicrobial activity of ceftolozane/tazobactam tested against *Pseudomonas aeruginosa* and Enterobacteriaceae with various resistance patterns isolated in European hospitals (2011-12). J Antimicrob Chemother 2014;69:2713–22. https://doi.org/10.1093/jac/dku184.

[5] Ge Y, Whitehouse MJ, Friedland I, Talbot GH. Pharmacokinetics and safety of CXA-101, a new antipseudomonal cephalosporin, in healthy adult male and female subjects receiving single- and multiple-dose intravenous infusions. Antimicrob Agents Chemother 2010;54:3427–31. https://doi.org/10.1128/AAC.01753-09.

[6] Miller B, Hershberger E, Benziger D, Trinh M, Friedland I. Pharmacokinetics and safety of intravenous ceftolozane-tazobactam in healthy adult subjects following single and multiple ascending doses. Antimicrob Agents Chemother 2012;56:3086–91. https://doi.org/10.1128/AAC.06349-11.

[7] Chandorkar G, Xiao A, Mouksassi MS, Hershberger E, Krishna G. Population pharmacokinetics of ceftolozane/tazobactam in healthy volunteers, subjects with varying degrees of renal function and patients with bacterial infections. J Clin Pharmacol 2015;55:230–9. https://doi.org/10.1002/jcph.395.

[8] Craig WA. D.R. Andes. In vivo activities of ceftolozane, a new cephalosporin, with and without tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae, including strains with extended-spectrum β-lactamases, in the thighs of neutropenic mice. Antimicrob Agents Chemother 2013;57:1577–82. https://doi.org/10.1128/AAC.01590-12.

[9] U.S. Prescribing Information: ZERBAXA (ceftolozane and tazobactam) for injection, for intravenous use. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206829lbl.pdf [Accessed 23 August 2018].

[10] Aiudi A, Miller B, Krishna G, Adedoyin A, Xiao A. Pharmacokinetics, safety, and tolerability of ceftolozane/tazobactam in healthy Japanese, Chinese, and white subjects. Fundam Clin Pharmacol 2016;30:625–33. https://doi.org/10.1111/fcp.12227.

[11] Arakawa S, Kawahara K, Kawahara M, Yasuda M, Fujimoto G, Sato A, et al. The efficacy and safety of tazobactam/ceftolozane in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection. J Infect Chemother 2019;25:104–10.

[12] Mikamo H, Monden K, Miyasaka Y, Horiuchi T, Fujimoto G, Fukuhara T, et al. The efficacy and safety of tazobactam/ceftolozane in Japanese patients with complicated intra-abdominal infections (cIAI). J Infect Chemother 2019;25:111–6.
[13] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41. https://doi.org/10.1159/000180580.
[14] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92. https://doi.org/10.1053/j.ajkd.2008.12.034.
[15] Yu B, Adedoyin A, Hershberger E, Caro L, Xiao A, Rhee EG, et al. Safety, tolerability, and pharmacokinetics of 3 g of cefolotozane/tazobactam in health adults: a randomized, placebo-controlled, multiple-dose study. Clin Pharmacol Drug Dev 2018;7:382–91. https://doi.org/10.1002/cpdd.429.
[16] Larson KB, Patel YT, Willavize S, Rizk ML, Yu B, Johnson MG, et al. Ceftolozane/tazobactam dose selection for pediatric patients (birth to <18 years). Fort Lauderdale, FL: American Conference on Pharmacometrics (ACoP8); 2017;October 15-18. https://www.simulations-plus.com/resource/ceftolozane-tazobactam-dose-selection-pediatric-patients-birth/ [Accessed 23 August 2018].
[17] VanScoy B, Mendes RE, Nicasio AM, Castanheira M, Bulik CC, Okusanya OO, et al. Pharmacokinetics-pharmacodynamics of tazobactam in combination with ceftolozane in an in vitro infection model. Antimicrob Agents Chemother 2013;57:2809–14. https://doi.org/10.1128/AAC.02513-12.
[18] Xiao AJ, Caro L, Popejoy MW, Huntington JA, Kullar R. PK/PD target attainment with ceftolozane/tazobactam using Monte Carlo simulation in patients with various degrees of renal function, including augmented renal clearance and end-stage renal disease. Infect Dis Ther 2017;6:137–48. https://doi.org/10.1007/s40121-016-0143-9.
[19] Wooley M, Miller B, Krishna G, Hershberger E, Chandorkar G. Impact of renal function on the pharmacokinetics and safety of ceftolozane-tazobactam. Antimicrob Agents Chemother 2014;58:2249–55. https://doi.org/10.1128/AAC.02151-13.