CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 206-494	Submission Date(s): 06/25/2014
Drug	Ceftazidime-Avibactam
Trade Name	AVICAZ® Injection
OCP Reviewers	Seong H, Jang, Ph.D.
OCP Team Leader	Kimberly Bergman, Pharm.D.
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OCP Division	DCP4
OND Division	DAIP
Sponsor	Cerexa, Inc
Relevant IND(s)	IND 101,307
Submission Type; Code	Original; 1S; Priority Review
Formulation; Strength(s)	Powder for IV Injection (2 g ceftazidime and 0.5 g avibactam) in a single-use, clear glass vial
Indication	Treatment of infections proven or suspected to be caused by AVICAZ-susceptible organisms (including ceftazidime resistant, β-lactamase-producing, Gram-negative bacteria) in the following indications: • Complicated Intra-abdominal Infection • Complicated Urinary Tract Infection, including Acute Pyelonephritis • Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options in patients ≥ 18 years of age
Dosage and Administration	2.5 g (2 g ceftazidime and 0.5 g avibactam) administered every 8 hours by intravenous (IV) infusion over 2 hours

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1. Executive Summary

The sponsor submitted this NDA for the use of ceftazidime in combination with avibactam (CAZ-AVI) in the treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI). The recommended dosage of CAZ-AVI is 2.5 g (2 g ceftazidime + 0.5 g avibactam) administered every 8 hours (q8h) by intravenous (IV) infusion over 2 hours in patients ≥ 18 years of age with normal renal function or mild renal impairment (creatinine clearance [CRCL] > 50 mL/min). Dose adjustments for patients with moderate and severe renal impairment and patients with end-stage renal disease requiring hemodialysis are recommended (see below).

Ceftazidime, the bactericidal β-lactam component of CAZ-AVI, is approved for the treatment of bacterial infections caused by susceptible pathogens. Included among these are cUTI caused by *Pseudomonas aeruginosa*, *Enterobacter spp.*, *Proteus spp.*, *Klebsiella spp.*, and *Escherichia coli* and serious intra-abdominal infections, including peritonitis, caused by *E. coli*, *Klebsiella spp.*, *Staphylococcus aureus* (methicillin-susceptible strains), and polymicrobial infections caused by aerobic and anaerobic organisms. Resistance to cephalosporins due to β-lactamase-producing bacteria is increasing in various regions worldwide. Avibactam, a β-lactamase inhibitor, is intended to extend the activity of ceftazidime to include Gram-negative bacteria that are non-susceptible to ceftazidime alone due to the production of a β-lactamase.

As a β-lactamase inhibitor, avibactam has a spectrum of activity against Ambler class A extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase class A (KPC) enzymes, Ambler class C enzymes, and some class D β-lactamases. Avibactam has no meaningful antibacterial activity at achievable concentrations in humans. Avibactam is not approved in any markets worldwide. Clinical studies have been conducted with avibactam in combination with ceftazidime, ceftaroline fosamil, and aztreonam.

The clinical development program for CAZ-AVI includes 10 completed Phase 1 clinical pharmacology studies, 1 completed Phase 2 study in patients with cUTI, and 1 completed Phase 2 study in patients with cIAI. In addition, avibactam pharmacokinetic (PK) data from 4 completed Phase 1 clinical pharmacology studies in the ceftaroline fosamil-avibactam (CXL) development program are included in this submission.

The proposed dosing regimens provides ~100% of the probability of the PK/PD targets (i.e., 50%fT > MIC for ceftazidime and 50%fT > 1.0 mg/L) at up to 8 µg/mL of CAZ-AVI MIC (i.e., measured using a fixed concentration of avibactam of 4 mg/L). Together with the efficacy results of Phase 2 studies, the proposed dosing regimen of CAZ-AVI appears to be appropriate for organisms with MIC values up to 8 µg/mL of CAZ-AVI MIC. However, the originally proposed dosing regimens for patients with moderate or severe renal impairment are recommended to be revised because (a) the ongoing Phase 3 cIAI study showed a lower clinical cure rate in patients with moderate (CrCL 31-50 mL/min) renal impairment who received the originally proposed dosing regimen and (b) the originally proposed dosing regimens are predicted to result in substantially lower exposure of ceftazidime and avibactam in moderate and severe renal impairment patients compared with patients with normal renal function.

1.1. Recommendation

From a Clinical Pharmacology perspective, we support the approval of AVICAZ injection for the proposed indications in patients ≥ 18 years of age. However, we recommend the originally proposed dosing regimens for patients with moderate and severe renal impairments be revised as follows.

Estimated Creatinine Clearance (mL/min)[a]	***Recommended Dosage Regimen for AVICAZ***
> 30 to ≤ 50	1.25 g (1.0 g ceftazidime + 0.25 g avibactam) IV (over 2 hours) every 8 hours
> 15 to ≤ 30	0.94 g (0.75 g ceftazidime + 0.188 g avibactam) IV (over 2 hours) every 12 hours
> 5 to ≤ 15[b]	0.94 g (0.75 g ceftazidime + 0.188 g avibactam) IV (over 2 hours) every 24 hours
≤ 5[b]	0.94 g (0.75 g ceftazidime + 0.188 g avibactam) IV (over 2 hours) every 48 hours
[a] As calculated using the Cockcroft-Gault formula. [b] Both ceftazidime and avibactam are hemodialyzable; thus, AVICAZ should be administered after hemodialysis on hemodialysis days.	

1.2. Phase 4 Commitments

- Conduct a study to evaluate the efficacy and safety of the alternatively recommended dosages of AVYCAZ in patients with complicated intra-abdominal infection with CRCL ≤50 mL/min.

1.3. Summary of Important Clinical Pharmacology findings

Summary of Pharmacokinetics

The PK of ceftazidime and avibactam are linear, with C_{max} and AUC increasing in proportion to dose. Both avibactam and ceftazidime undergo limited metabolism and there is no evidence of a drug-drug interaction (DDI) between ceftazidime and avibactam. No appreciable accumulation of ceftazidime or avibactam was observed after multiple dose administration of CAZ-AVI for 11 days. Both ceftazidime and avibactam are eliminated primarily by the kidney, with the majority of the dose (80-90% ceftazidime and 85% avibactam) recovered as unchanged drug in urine. The terminal elimination half-life (T½) of ceftazidime and of avibactam is approximately 2 h in patients with normal renal function and substantially prolonged in patients with renal impairment, necessitating reduction of dose and prolongation of the dosing interval in patients with creatinine clearance (CrCL) less than 50 mL/min. A Phase 1 study conducted with CAZ-AVI in healthy adult subjects demonstrated that ceftazidime and avibactam are able to penetrate into bronchial epithelial lining fluid (ELF) to a similar extent and with similar kinetics. The exposure of both drugs in the lung was approximately 30-35% of the exposure in plasma. Less than 10% of ceftazidime is protein bound. The degree of protein binding is independent of concentration. The binding of avibactam to human plasma proteins is also low (5.7% to 8.2%) and similar across the range of concentrations tested in vitro (0.5 to 50 mg/L).

The potential for DDIs with CAZ-AVI is low based on the following: both ceftazidime and avibactam undergo limited metabolism; avibactam showed no significant inhibition or induction of cytochrome P450 (CYP) enzymes in vitro, and ceftazidime also showed no CYP induction potential; both avibactam and ceftazidime have low binding to human plasma proteins; and,

avibactam and ceftazidime did not inhibit any major renal or hepatic transporters in vitro in the clinically relevant exposure range. Avibactam was shown to be a substrate of human organic anion transporter (OAT)1 and OAT3 in vitro, which may contribute to its active secretion by the kidneys. In vitro uptake of avibactam by OAT1 and OAT3 was not inhibited by ceftazidime but was inhibited (by 56% to 70%) by probenecid, a potent OAT inhibitor. The clinical impact of potent OAT inhibitors on the PK of avibactam is not known.

Data from Phase 1 studies demonstrated that there was no PK interaction between ceftazidime and avibactam, and no PK interaction between ceftaroline fosamil and avibactam. In addition, a Phase 1 study showed no PK interaction between CAZ-AVI and metronidazole.

Population Pharmacokinetics of CAZ-AVI

Population PK analyses have been conducted for both avibactam and ceftazidime based on a pooled plasma concentration dataset from the Phase 2 cIAI study (NXL104/2002), five Phase 1 clinical pharmacology studies in healthy volunteers, and subjects with impaired renal function (CAZ-MS-01). The analysis demonstrated that the main predictors of clearance (CL) for avibactam and ceftazidime were body surface-normalized creatinine clearance (nCrCl) and CrCl, respectively, consistent with the predominant renal excretion of both compounds. In addition, cIAI was identified as a significant covariate impacting clearance and central volume of distribution of both avibactam and ceftazidime. The typical values of avibactam CL and central volume of distribution were higher in the cIAI population compared to healthy volunteers. The population PK model predicted a 34% and 59% decrease in the mean steady state AUC and C_{max} for avibactam, respectively, for Phase 2 cIAI subjects with normal renal function compared to Phase 1 subjects with normal renal function. Similarly, typical values of ceftazidime CL and central volume of distribution were higher in the cIAI population compared to healthy volunteers. The population PK model predicted a 20% and 38% decrease in the mean steady state AUC and C_{max} for ceftazidime, respectively, for Phase 2 cIAI subjects with normal renal function compared to Phase 1 subjects with normal renal function.

CAZ-AVI PK/PD Target Attainment Analyses

The population PK models for ceftazidime and avibactam were used to explore PK/PD relationships in the Phase 2 studies and to conduct simulations to evaluate the probability of joint PK/PD target attainment for ceftazidime and avibactam. The percent target attainment (PTA) analyses were used to support proposed breakpoints and to indirectly support the efficacy of CAZ-AVI against ceftazidime- nonsusceptible microorganisms.

Determination of PK/PD targets: The percent time that free-drug concentrations are above the minimum inhibitory concentration (MIC) over a dose interval (% fT > MIC) was established as the PK/PD index associated with the efficacy of CAZ in literature. The percent time of free-drug concentrations that are above a threshold concentration (C_T) over a dose interval (% fT > C_T) was determined to be associated with the efficacy of AVI in restoring CAZ activity/efficacy based on hollow-fiber and animal model experiments.

The magnitude of the PK/PD index for antimicrobial efficacy (PK/PD target) for CAZ was reported to be approximately 40% to 50% fT > MIC for infections due to *Staphylococcus aureus, Streptococcus pneumoniae,* and *Enterobacteriaceae.*

The PK/PD target of avibactam was determined in restoring the activity of ceftazidime against infecting, ceftazidime-resistant *P. aeruginosa* in neutropenic mouse thigh and lung infection models. With background dosing of ceftazidime which would just allow maximal growth for each isolate, the dose of avibactam was titrated by amount and frequency in an analogous way to dose-variation and fractionation. In a neutropenic thigh mouse model, the %fT > 1 mg/L that provided bacterial stasis was measured in co-dosing experiments (i.e. avibactam dosed simultaneously with ceftazidime q2h) with 6 isolates of ceftazidime-resistant *P. aeruginosa*. The arithmetic mean avibactam %fT > 1 mg/L was 40.2% for stasis. The mean magnitude associated with 1-log kill was 50.3%. Three isolates responded with 2-log kill at avibactam fT > 1 mg/L of 45.0-48.4%.

The mean magnitude of avibactam %fT > 1 mg/L associated with stasis and 1- and 2-log kills of four ceftazidime-resistant *P. aeruginosa* isolates infecting the lungs of neutropenic CD-1 female mice in the background of 2-hourly dosing of ceftazidime was 20.2%, 24.0% and 30.3%, respectively.

Collectively, 50% fT > 1.0 mg/L was used as the PK/PD target for avibactam to restore the activity of ceftazidime against infecting, ceftazidime-resistant, *P. aeruginosa*.

PK/PD Target Attainment: PK/PD target attainment analyses demonstrated > 90% joint target attainment with the proposed labeled dose of CAZ-AVI (2.5 g; 2.0 g ceftazidime + 0.5 g avibactam q8h) infused over 2 h at MICs up to 8 mg/L (Table 1). The population PK models used in the simulations included subject effects on the clearance of both ceftazidime and avibactam, with cIAI subjects having faster clearance (and thus lower plasma exposure) than healthy subjects or cUTI subjects. The PTA for cUTI subjects is therefore higher than the PTA presented in Table 1 for cIAI subjects.

Table 1. Percentage of simulated cIAI subjects achieving PK/PD targets at the proposed dose of CAZ-AVI infused q8h over 2 h

CAZ-AVI MIC (mg/L)	***Percentage of Simulated Subjects Achieving PK/PD Target*** [a, b]
2	98.9
4	98.9
8	98.1
16	50.8
32	1.3

[a]: 5000 simulated cIAI subjects with normal renal function (CrCL > 80 mL/min).
[b]: PK/PD target for ceftazidime is 50% fT > CAZ-AVI MIC and for avibactam is 50% fT > 1 mg/L.

Dose Adjustments for Patients with Renal Impairment

Although the predicted exposure (i.e., C_{max} and AUC) of ceftazidime and avibactam in the simulated patients with moderate (31 mL/min ≤ CrCL ≤ 50 mL/min) and severe [SEV1 (16 mL/min ≤ CrCL ≤ 30mL/min) and SEV2 (6 mL/min ≤ CrCL ≤ 15 mL/min)] renal impairments receiving the proposed dosing regimen were substantially lower compared with the simulated patients with normal renal function (Table 2), the originally proposed dosing regimen for patients with different renal function provides ~100% of the probability of the PK/PD target (i.e., 50%*f*T

> MIC for ceftazidime and 50%*f*T > 1.0 mg/L) at up to 8 µg/mL of MIC (see Table 15 in section **2.2.4.1**). Thus, the originally proposed dosing regimens for patients with renal impairment were initially deemed acceptable. However, in an ongoing Phase 3 study, it was reported that cIAI patients with moderate renal impairment (i.e., estimated creatinine clearance [CrCL] ≤ 50 mL/min) at study baseline treated with CAZ-AVI had a lower clinical cure rate compared with patients treated with meropenem (Table 3).

Table 2. Summary of PK parameter values (Mean±SD) in simulated cIAI subject population for different renal function groups (5000 simulated subjects per group) with CAZ-AVI given as a 2-hour IV infusion

Renal Function	Proposed Dose Regimen	Ceftazidime		Avibactam	
		$C_{max,ss}$ (µg/mL)	$AUC_{0-24,ss}$ (µg·h/mL)	$C_{max,ss}$ (µg/mL)	$AUC_{0-24,ss}$ (µg·h/mL)
NORM	2000 mg CAZ + 500 mg AVI, q8h	47.2±13.4	542±161	9.31±1.87	93.5±21.3
MILD	2000 mg CAZ + 500 mg AVI, q8h	59.9±17.1	828±260	11.2±2.37	131±36.4
MODE	1000 mg CAZ + 250 mg AVI, q12h	33.5±9.6	448±142	6.84±1.48	80.3±22.8
SEV1	1000 mg CAZ + 250 mg AVI, q24h	33.9±10.2	400±136	7.61±1.85	82.8±26.7
SEV2	500 mg CAZ + 125 mg AVI, q24h	27.0±9.03	455±180	6.79±2.07	116±47.6
ESRD	500 mg CAZ + 125 mg AVI, q48h	45.7±22.9	898±527	5.26±1.04	75.6±16.8

NORM Normal renal function (CrCL > 80 mL/min); MILD Mild renal impairment (50 mL/min < CrCL ≤ 80 mL/min); MODE Moderate real impairment (30 mL/min < CrCL ≤ 50 mL/min); SEV1 Severe renal impairment (15 mL/min < CrCL ≤ 30mL/min); SEV2 Severe renal impairment (5 mL/min < CrCL ≤ 15 mL/min); ESRD End-stage renal disease (CrCL ≤ 5 mL/min).

Table 3. Summary of clinical cure rate at test of cure, by baseline renal function subgroup [Phase 3 cIAI Study (Studies 4280C00001 and 4280C00005); mMITT Analysis Set)]

Baseline Renal Function Subgroup	***CAZ-AVI + MTZ n/N1 (%)***	***Meropenem n/N1 (%)***
Normal function/mild impairment (CrCL > 50 mL/min)	322/379 (85)	321/373 (86)
Moderate impairment (CrCL > 30 to ≤ 50 mL/min)	14/31 (45)	26/35 (74)

mMITT = microbiologically Modified Intent-to-Treat; MTZ = metronidazole; n = number of patients with clinical cure; N1 = total number of patients.

Collectively, the dosing regimens of CAZ-AVI for patients with <50 mL/min of CrCL are recommended to be revised because of (a) a lower clinical cure rate in patients with moderate renal impairment receiving the proposed CAZ-AVI dosing regimen, (b) substantially lower ceftazidime and avibactam exposure in patients with moderate and severe renal impairment compared to patients with normal renal function, and (c) FORTAZ label that allows for a 50% increase in ceftazidime dose for renally impaired patients with severe infections. The revised dosing regimens of CAZ-AVI for patients with renal impairments (see section **1.1**) are predicted to provide patients with ≤50 mL/min of CrCL with comparable exposure of ceftazidime and avibactam to patients with normal renal function receiving 2000 mg CAZ + 500 mg AVI Q8h, but still lower than patients with mild renal impairment receiving 2000 mg CAZ + 500 mg AVI Q8h (Figure 1). Additionally, because the exposure of both ceftazidime and avibactam is highly dependent on renal function, it is recommended to monitor CrCL frequently and adjust the CAZ-AVI dose for the patients presumed to improve renal function rapidly during the period of drug treatment.

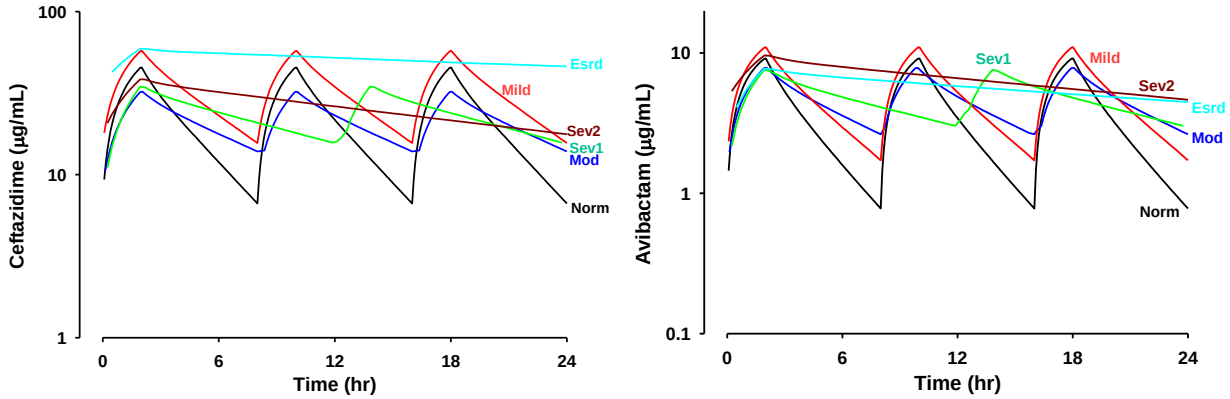

Figure 1. Steady-state concentration-time profiles of ceftazidime (right panel) and avibactam (left panel) in simulated patients with different renal function receiving the revised dosing regimen: Normal (CrCL >80 mL/min, black line): 2000 mg CAZ + 500 mg AVI, q8h; Mild (CrCL 51-80 mL/min, red line): 2000 mg CAZ + 500 mg AVI, q8h); Moderate (CrCL 31-50 mL/min, blue line): 1000 mg CAZ + 250 mg AVI, q8h); SEV1 (CrCL 16-30 mL/min, green line): 750 mg CAZ + 188 mg AVI, q12h); SEV2 (CrCL 6-15 mL/min, dark red line): 750 mg CAZ + 188 mg AVI, q24h); ESRD (CrCL 0-5 mL/min, sky blue line): 750 mg CAZ + 188 mg AVI, q48h). N=5000 per each group. Lines represent the median values.

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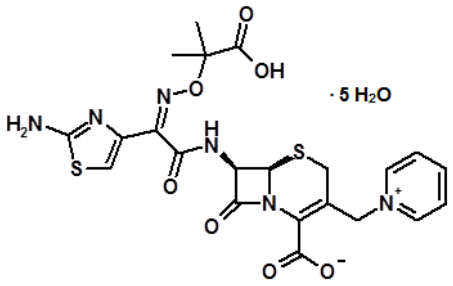
2. Question-Based Review

2.1. General attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

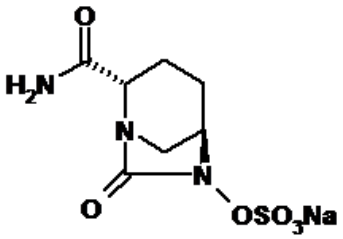
AVICAZ is an antibacterial combination product consisting of the semisynthetic antibiotic ceftazidime pentahydrate and the β-lactamase inhibitor avibactam sodium for intravenous administration.

Ceftazidime
Ceftazidime is a semisynthetic, broad-spectrum, β-lactam antibiotic. It is the pentahydrate of (6R,7R,Z)-7-(2-(2-aminothiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetamido)-8-oxo-3-(pyridinium-1-ylmethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate. Its molecular weight is 636.6. The empirical formula is $C_{22}H_{32}N_6O_{12}S_2$.



Chemical structure of ceftazidime pentahydrate

Avibactam
Avibactam sodium chemical name is sodium [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate. Its molecular weight is 287.23. The empirical formula is $C_7H_{10}N_3O_6SNa$.



Chemical structure of avibactam sodium

AVICAZ parenteral combination is a white to yellow sterile powder consisting of ceftazidime pentahydrate and avibactam sodium packaged in glass vials. The formulation also contains sodium carbonate. Each AVICAZ 2.5 g single-dose vial contains sterile ceftazidime pentahydrate/sodium carbonate equivalent to 2 g of ceftazidime and sterile avibactam sodium

equivalent to 0.5 g avibactam. The total sodium content of the mixture is approximately 146 mg (6.4 mEq)/vial.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

AVICAZ is a combination product consisting of a cephalosporin-class antibacterial agent, ceftazidime, and a β-lactamase inhibitor, avibactam.

Like other β-lactam compounds, ceftazidime inhibits of cell wall synthesis by inhibiting enzymes (the high-molecular-weight penicillin-binding proteins: PBPs) involved in the biosynthesis and cross-linking of peptidoglycan.

Avibactam, a non-β-lactam β-lactamase inhibitor, inactivates a wide variety of β-lactamases including: Ambler Class A extended-spectrum β-lactamases (ESBLs, eg, TEM, SHV, and CTX-M families); Class A serine carbapenemases (KPCs); Class C cephalosporinases (AmpC), and some Class D β-lactamases (e.g., OXA-48). Avibactam does not induce AmpC β-lactamases. Avibactam protects ceftazidime from degradation by β-lactamase enzymes and extends the antibiotic spectrum of ceftazidime to include many Gram-negative bacteria normally not susceptible to ceftazidime.

The proposed indications are the treatment of infections proven or suspected to be caused by AVICAZ-susceptible organisms (including ceftazidime-resistant, β-lactamase-producing, Gram-negative bacteria) in the indications listed below.

- Complicated Intra-abdominal Infection (cIAI)

Complicated intra-abdominal infections (in combination with metronidazole) caused by *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, Pseudomonas aeruginosa,* and *Pseudomonas stutzeri*; and polymicrobial infections caused by aerobic and anaerobic organisms including *Bacteroides* spp., (many strains of *Bacteroides fragilis* are resistant to AVICAZ).

- Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP)

Complicated urinary tract infections, including acute pyelonephritis, caused by *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Citrobacter freundii*, *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus,* and *Pseudomonas aeruginosa*.

- Limited Use Indication

Aerobic Gram-negative Infections with Limited Treatment Options
AVICAZ may be used for Hospital-acquired Bacterial Pneumonia (HABP)/Ventilator-associated Bacterial Pneumonia (VABP) and Bacteremia where limited or no alternative therapies are available and the infection is proven or suspected to be caused by the following AVICAZ-susceptible organisms, including ceftazidime-resistant, β-lactamase-producing, Gram-negative bacteria: *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Pseudomonas aeruginosa, Pseudomonas stutzeri, Providencia stuartii, Citrobacter freundii, Citrobacter koseri, Serratia*

spp., *Enterobacter aerogenes*, *Enterobacter cloacae*, and *Proteus* spp., including *Proteus mirabilis* and indole-positive *Proteus.*

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dosage of AVICAZ is 2.5 g (2 g ceftazidime and 0.5 g avibactam) administered every 8 hours by intravenous (IV) infusion over 2 hours in patients ≥ 18 years of age. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress. For treatment of cIAI, metronidazole should be given concurrently. The guidelines for dosage of AVICAZ are listed in Table 4.

Table 4. Dosage of AVICAZ by infection

Infection	**Dosage**	**Frequency**	**Infusion Time (hours)**	**Recommended Duration of Total Antimicrobial Treatment**
Complicated Intra-abdominal Infection [used in combination with metronidazole]	2.5 g	Every 8 hours	2	5 to 14 days
Complicated Urinary Tract Infection including Acute Pyelonephritis	2.5 g	Every 8 hours	2	7 to 14 days
Limited Use Indication: Hospital-acquired Bacterial Pneumonia (HABP)/Ventilator-associated Bacterial Pneumonia (VABP) and Bacteremia where limited or no alternative therapies are available and the infection	(b) (4)			

[a] Total duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress.

The recommended dosage of AVICAZ in patients with renal impairment is presented in Table 5. Please note that this recommended dosage of AVICAZ in patients with renal impairment is recommended to be revised (see section **2.2.4.4** and **2.3** Renal Impairment)

Table 5. Dosage of AVICAZ in patients with renal impairment

Estimated Creatinine Clearance (mL/min)[a]	***Recommended Dosage Regimen for AVICAZ***
> 50	No dosage adjustment necessary
> 30 to ≤ 50	1.25 g (1 g ceftazidime + 0.25 g avibactam) IV (over 2 hours) every 12 hours
> 15 to ≤ 30	1.25 g (1 g ceftazidime + 0.25 g avibactam) IV (over 2 hours) every 24 hours
> 5 to ≤ 15[b]	0.625 g (0.5 g ceftazidime + 0.125 g avibactam) IV (over 2 hours) every 24 hours
≤ 5[b]	0.625 g (0.5 g ceftazidime + 0.125 g avibactam) IV (over 2 hours) every 48 hours

[a] As calculated using the Cockcroft-Gault formula.
[b] Both ceftazidime and avibactam are hemodialyzable; thus, AVICAZ should be administered after hemodialysis on hemodialysis days.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Thirteen clinical studies of CAZ-AVI or avibactam alone have been completed. This includes 11 completed Phase 1 Clinical Pharmacology studies (10 from the CAZ-AVI development program, and 1 from the ceftaroline fosamil-avibactam [CXL] program) and 2 completed Phase 2 efficacy and safety studies, one each in cIAI and cUTI. Additionally, there are 8 ongoing CAZ-AVI studies. Completed and ongoing studies of CAZ-AVI or avibactam alone are listed in Table 6 and Table 7, respectively.

Table 6. Completed clinical studies

Study ID	Study Type/Population
Clinical Pharmacology Studies with CAZ-AVI or Avibactam Alone	
NXL104/1001	Single-dose escalation PK/Healthy adults
NXL104/1002	Multiple-dose escalation PK/Healthy adults
NXL104/1003	Single-dose PK avibactam, renal impairment/Healthy adults
NXL104/1004	Single-dose PK avibactam, age and gender/Healthy adults
D4280C00007	Thorough QT/Healthy adults
D4280C00008	DME/Healthy adults
D4280C00009	ELF/Healthy adults
D4280C00010	Single- and multiple-dose PK, Japanese subjects/Healthy adults
D4280C00011	DDI PK, ceftazidime and avibactam/Healthy adults
D4280C00012	DDI PK, metronidazole/Healthy adults
Clinical Pharmacology Study with Avibactam Alone (From CXL development program)	
CXL-PK-01	DDI PK, ceftaroline and avibactam/Healthy adults
Phase 2 Clinical Efficacy and Safety Studies	
NXL104/2001	cUTI/Infected hospitalized adults
NXL104/2002	cIAI/Infected hospitalized adults

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection;
DDI = drug-drug interaction; DME = distribution, metabolism, and excretion; ELF = epithelial lining fluid;
PK = pharmacokinetic; QT = QT interval.

Table 7. Ongoing clinical studies

Study ID	Study Type/Population	Blinded
Phase 3 Clinical Efficacy and Safety Studies		
D4281C00001	HABP/VABP/Infected hospitalized adults	yes
D4280C00001/5	cIAI/Infected hospitalized adults	yes
D4280C00002/4	cUTI/Infected hospitalized adults	yes
D4280C00006	Resistant Pathogen: cIAI and cUTI/Infected hospitalized adults	no
D4280C00018	cIAI (Asia)/Infected hospitalized Chinese adults	yes
Clinical Pharmacology Studies with CAZ-AVI		
D4280C00014	Single-dose PK/Infected pediatric patients	no
D4280C00020	Single- and multiple-dose PK (China)/Healthy adults	yes
D4280C00023	Multiple-dose, effect on intestinal flora (CAZ-AVI and CXL)/Healthy	no

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Complicated Intra-abdominal Infection (cIAI) Trial

A total of 204 adults with clinically documented cIAI were enrolled in a randomized, multicenter, multinational, double-blind trial comparing CAZ-AVI 2.5 g (2 g ceftazidime and 0.5 g avibactam) administered IV over 30 minutes plus 0.5 g metronidazole administered IV over 1 hour every 8 hours to 1 g meropenem administered IV over 30 minutes every 8 hours. Treatment duration was 5 to 14 days. A switch to oral therapy was not allowed.

The Microbiologically Modified Intent-to-Treat (mMITT) Population included all patients who received at least one dose of study therapy according to their randomized treatment group, met minimal disease criteria for cIAI, and had at least one bacterial pathogen. The Microbiologically Evaluable (ME) Population included all patients who met minimal disease criteria for cIAI (confirmed by operative findings), demonstrated sufficient adherence to the protocol, and had at least one pathogen that was susceptible to both study treatments.

The primary efficacy endpoint to evaluate the effect of CAZ-AVI for the treatment of cIAI was the clinical cure rates at the Test-of-Cure (TOC) visit (2 weeks after completion of therapy) in the mMITT and ME Populations for the cIAI trial (Table 8). Analyses were also conducted reporting the clinical cure rates by pathogen at the TOC visit in the mMITT Population from the cIAI trial (Table 9).

Table 8. Clinical cure rates at TOC from the cIAI trial (Study NXL104/2002)

	CAZ-AVI plus metronidazole n/N (%)	***Meropenem n/N (%)***	***Treatment Difference (2-sided 95% CI)***
mMITT	70/85 (82.4)	79/89 (88.8)	-6.4 (-17.3, 4.2)
ME	62/68 (91.2)	71/76 (93.4)	-2.2 (-12.3, 7.0)

Table 9. Clinical cure rates by pathogen at TOC from the cIAI trial, mMITT population (Study NXL104/2002)

	CAZ-AVI plus metronidazole n/N (%)	***Meropenem n/N (%)***
Aerobic Gram-negative Pathogens:		
Enterobacteriaceae	57/70 (81.4)	64/74 (86.5)
Escherichia coli	49/60 (81.7)	55/62 (88.7)
Klebsiella pneumoniae	6/8 (75.0)	11/13 (84.6)
Enterobacter cloacae	1/1 (100.0)	4/5 (80.0)
Klebsiella oxytoca	2/2 (100.0)	2/2 (100.0)
Proteus mirabilis	1/2 (50.0)	1/1 (100.0)
Providencia stuartii	1/1 (100.0)	0/0
Pseudomonas aeruginosa	6/6 (100.0)	5/5 (100.0)
Pseudomonas stutzeri	1/1 (100.0)	0/0
Pseudomonas spp.	1/1 (100.0)	0/0
Anaerobic Pathogens:		
Bacteroides fragilis	3/7 (42.9)	3/4 (75.0)
Bacteroides caccae	2/2 (100.0)	0/1 (0.0)
Bacteroides uniformis	2/2 (100.0)	1/1 (100.0)

Complicated Urinary Tract Infection (cUTI), including Acute Pyelonephritis (AP) Trial
A total of 137 adults with clinically documented cUTI, including AP, were enrolled in a randomized, multicenter, multinational, investigator-blinded trial comparing CAZ-AVI 0.625 g (0.5 g ceftazidime and 0.125 g avibactam) administered IV over 30 minutes every 8 hours to 0.5 g imipenem cilastin administered IV over 30 minutes every 6 hours. Treatment duration was 7 to 14 days. A switch to oral therapy was allowed after at least 4 days of IV therapy.

The mMITT Population included all patients who received at least one dose of study therapy according to their randomized treatment group and had a study-qualifying pretreatment urine culture containing > 10^5 CFU/mL of at least one uropathogen. The ME Population was a subset of the patients in the mMITT Population who met minimal disease criteria for cUTI, who demonstrated sufficient adherence to the protocol, had a microbiological assessment of the urine at the TOC visit, and had at least one uropathogen susceptible to study therapy.

The primary efficacy endpoint to evaluate the effect of CAZ-AVI for the treatment of cUTI, including AP, was microbiological eradication rates at the TOC visit (5 to 9 days after completion of therapy) in the mMITT and ME Populations for the cUTI trial (Table 10). Analyses were also conducted reporting the microbiological eradication rates by pathogen at the TOC visit in the mMITT Population from the cUTI trial (Table 11).

Table 10. Microbiological eradication rates at TOC from the cUTI trial (NXL104/2001)

	CAZ-AVI n/N (%)	***Imipenem cilastin n/N (%)***	***Treatment Difference (2-sided 95% CI)***
mMITT	31/46 (67.4)	31/49 (63.3)	4.1 (-15.1, 22.9)
cUTI with AP	21/30 (70.0)	17/29 (58.6)	11.4 (-13.2, 34.8)
cUTI without AP	10/16 (62.5)	14/20 (70.0)	-7.5 (-37.8, 23.0)
ME	19/27 (70.4)	25/35 (71.4)	-1.1 (-24.3, 21.2)
cUTI with AP	13/18 (72.2)	14/19 (73.7)	-1.5 (-30.3, 27.2)
cUTI without AP	6/9 (66.7)	11/16 (68.8)	-2.1 (-40.4, 32.9)

Table 11. Microbiological eradication rates by pathogen at TOC from the cUTI trial, mMITT population

	CAZ-AVI n/N (%)	***Imipenem cilastin n/N (%)***
Aerobic Gram-negative Pathogens:		
Enterobacteriaceae	31/43 (72.1)	31/47 (66.0)
Escherichia coli	31/43 (72.1)	26/42 (61.9)
Citrobacter koseri	1/1 (100.0)	0
Pseudomonas aeruginosa	0/3 (0.0)[a]	0/2 (0.0)

[a] The dose of CAZ-AVI in this study was one fourth of the recommended dose of CAZ-AVI for cUTI.

(b) (4)

(b) (4)

2.2.3. Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

CAZ and AVI were the active moieties measured in human plasma in clinical pharmacology studies and clinical studies. There is no evidence that any CAZ and AVI metabolites are pharmacologically active. Because CAZ and AVI plasma protein binding is not concentration-dependent, total drug concentration (bound plus free) of CAZ and AVI were measured in human plasma.

2.2.4. Exposure-response

The exposure-response relationship for CAZ-AVI was evaluated using in vitro pharmacokinetic models, in vivo animal models of infection, population PK/PD analysis, and target attainment analysis using Monte Carlo simulations.

2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

Results from the population PK analysis were used to predict individual exposure metrics for CAZ-AVI in patients with cIAI and patients with cUTI and to explore the respective datasets for a possible exposure-response relationship. In both studies, for both the subset with a "favorable" overall microbiological response as well as the subset with an "unfavorable" overall microbiological response, a very high percentage (i.e., over 80%) of patients met the pre-specified joint PK/PD target. Furthermore, nearly all subjects were clustered near the high range (i.e., well over 50%) of %fT > MIC for ceftazidime (using the CAZ-AVI MIC) and %fT > CT for avibactam. Therefore, identification of PK/PD targets from the clinical data was not feasible, and no formal exposure-response model building was implemented for either dataset.

<u>Determination of the PK/PD index and target for ceftazidime</u>
It is well-established that the PK/PD index that best describes the antibacterial activity of ceftazidime is %fT > MIC. Values of 40-50% fT > MIC were associated with efficacy of ceftazidime in animal models with *Enterobacteriaceae* and *P. aeruginosa*, and in clinical data in subjects with nosocomial pneumonia from whom Gram-negative bacilli, including *P. aeruginosa* were cultured.

<u>Determination of the PK/PD index and target for avibactam</u>
The approach taken to obtaining experimental data to be able to model PK/PD of the ceftazidime-avibactam combination was based on the theoretical concept that the pharmacodynamic rationale of a β-lactamase inhibitor is to protect the β-lactam partner from β-lactamase-catalyzed hydrolysis with the consequence that the pharmacodynamics of the

combination would revert to the pharmacodynamics of the β-lactam. Specifically, if avibactam effectively inhibited β-lactamases, then the PK/PD of ceftazidime-avibactam would revert to the PK/PD of ceftazidime (i.e. related to T > MIC). Thus, the experimental approach was to define a 'critical' or 'threshold' concentration (C_T) of avibactam that would occur during the exponential decline of avibactam plasma concentrations during one dosing interval. This C_T was defined as the concentration of avibactam reached during the terminal phase below which the inhibition of β-lactamases was not sufficient to prevent growth in the presence of ceftazidime.

In a hollow-fiber model:
Figure 2 shows an example of how the avibactam C_T against β-lactamase-producing *Enterobacteriaceae* was determined using a hollow-fiber model. In a series of experiments, the concentration of ceftazidime was set constant at 16 mg/L or 8 mg/L to be in excess of the ceftazidime-avibactam MIC, but below that of ceftazidime, for all strains tested (Figure 1; Line a). In combination with the constant ceftazidime concentration, two different regimens of avibactam were used to achieve similar 24 hours avibactam area under the concentration-time curve (AUC_{0-24}) values, as follows:

- 24 hours continuous constant rate infusion (Figure 1; Line b)
- A single simulated human-like profile (Figure 1; Line c)

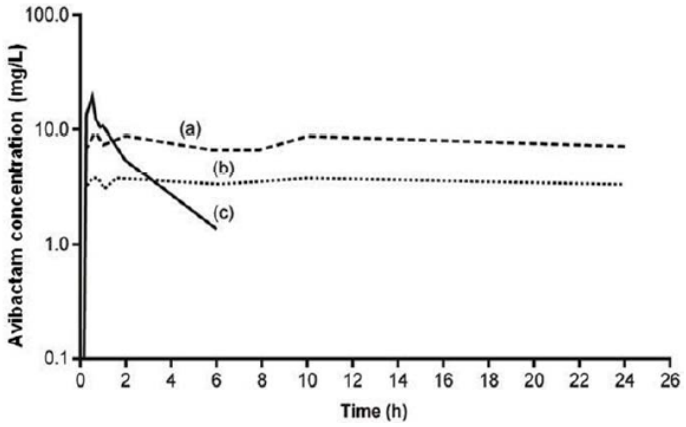


Figure 2. Example of concentration-time profiles of ceftazidime and avibactam in hollow-fiber experiments used to estimate a critical concentration (C_T) of avibactam. (a) ceftazidime (dashed line) was infused for 24 hours at a fixed concentration of 8 mg/L, while avibactam was either (b) infused at a fixed concentration of 1, 2 or 4 mg/L for 24 hours (4 mg/L in this example, dotted line) or (c) dosed to simulate a human-like profile (solid line) with α and β phase t½ values of 0.16 and 2.0 h, respectively, with roughly the same 24-h AUC as the avibactam continuous infusion.

Experiments in which human-like PK profiles of avibactam were simulated were used to estimate the threshold concentration (C_T) of avibactam during the exponentially-declining phase (Figure 2) below which inhibition of β-lactamase was lost, as inferred from the observation of bacterial re-growth in the presence of the continuous concentration of ceftazidime. Thus, the C_T was estimated as the minimum concentration of avibactam able to suppress growth of the β-lactamase-producing bacterium as judged by the concentration of avibactam in the hollow-fiber system at the time point when re-growth occurred. Values of C_T were experimentally estimated by extrapolation from the exponential-decline curves (Line c in Figure 2), because they occurred at times later than the decrease of avibactam concentrations to below the limit of quantitation.

In three experiments used in these estimations, ceftazidime was maintained at a constant background concentration of 8-10 mg/L while avibactam was instilled with simulated human-PK-like profiles with C_{max} values of 9, 31, or 37 mg/L, and exponential decline half-lives of 2 to 3 hours (Table 12). Viable counts were monitored in the perfused compartment, starting with inocula of 1-3 × 10^5 CFU/mL at time zero. In all three experiments, bacterial counts declined to below detectable limits in about 2 hours and stayed undetectable for a further 10 hours (i.e. confirmed experimentally at t = 12 h). After that, samples were not taken until t = 24 h, by which time growth had restarted (Figure 3 shows one example). The magnitude of C_T was estimated as being equal to or lower than the concentration of avibactam remaining in the hollow-fiber system at the time point at which growth suppression was last experimentally demonstrated. That time point was t = 12 hours in three experiments (as was the case in the experiment of Figure 3). As stated above, in these estimations, the concentration of avibactam at which regrowth occurred was below the limit of quantification, and so the concentration at the given time point was estimated by extrapolation of the mono-exponential decline of the terminal phase. Moreover, the estimate was made at the last time point when growth was experimentally confirmed to be suppressed, which was an indeterminate time before growth actually recurred. The concentration of avibactam estimated by this method was thus a maximum, so that the C_T reported here is less than or equal to the magnitude estimated at the given time point (Table 12). Table 12 provides 4 experimental estimates of C_T from hollow-fiber experiments with 3 β-lactamase-producing, ceftazidime-resistant, *Enterobacteriaceae*. The mean value was ≤ 0.21 mg/L (range ≤ 0.15 – ≤ 0.28 mg/L).

Table 12. Estimations of the 'critical' or 'threshold' concentration, C_T, of avibactam in hollow-fiber experiments

Species and strain	*β-Lactamase*	*MIC[a] (mg/L)*		*CAZ*		*AVI*		*Time at which C_T was estimated (h)*	*Estimated C_T (mg/L)*
		CAZ[a]	*CAZ-AVI[a]*	*Constant conc (mg/L)*	*AUC_{0-24} (mg.h.L^{-1})*	*C_{max} (mg/L)*	*AUC_{0-24} (mg.h.L^{-1})*		
E. cloacae 293HT96	Stably-derepressed AmpC	> 128	4	8.2	195	31.0	54.7	12	≤ 0.15[b]
K. pneumoniae 283CF5	SHV-5	64	2	8.3	198	8.9	16.4	12	≤ 0.22[b]
K. pneumoniae Tunisie K4	CTX-M-15; TEM-1[c]; OXA-1[c]	> 128	1	9.4–9.8	232	36.9	63.8	12	≤ 0.28[b]
E. cloacae 293HT96	Stably-derepressed AmpC	> 128	4	20	480	~60	126	18–20	~ 0.2[d]
Mean	-	-	-	-	-	-	-	-	≤ 0.21

[a]: MIC values were measured by broth microdilution with avibactam at a fixed concentration of 4 mg/L.
[b]: Magnitudes of C_T are expressed as '≤ ' the stated value, because each estimation was made at t = 12 h, the time of the last sample for which continued growth inhibition was demonstrated; whereas re-growth occurred at an indeterminate time later than that, but before t = 24 hours (Figure 2). That is, at the time when growth re-started, the avibactam concentration had declined to a lower, but indeterminate, level than that estimated at t = 12 h.
[c]: TEM-1 and OXA-1 β-lactamases do not hydrolyze ceftazidime to any great extent.
[d]: In this experiment, C_T was estimated between 18-20 h; that is, 2 hour sampling times allowed greater precision in identifying the time at which re-growth occurred. However, the avibactam declining concentrations were modeled rather than measured for this experiment and so the estimate of C_T is approximate.

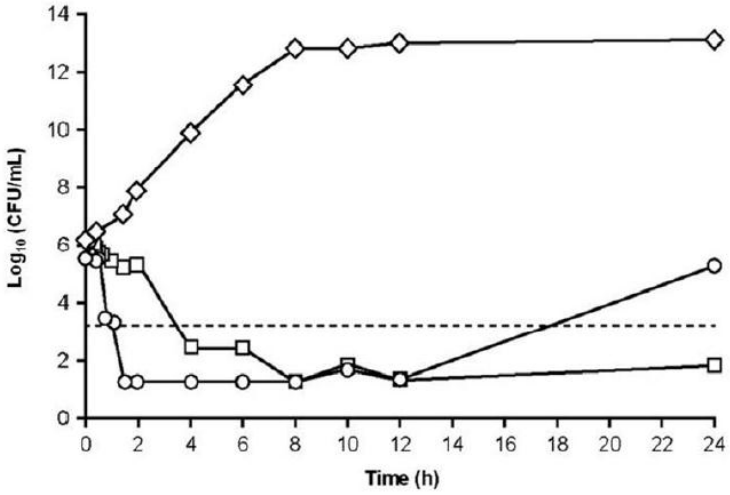


Figure 3. Responses of *E. cloacae* 293HT96 (stably derepressed *ampC*; ceftazidime MIC > 128 mg/L; ceftazidime-avibactam MIC 4 mg/L) to continuous infusion of ceftazidime combined with two different concentration-time profiles of avibactam in the hollow-fiber model. (◊) Growth control, in which the bacteria were exposed to neither ceftazidime nor avibactam. (□) Colony counts of *E. cloacae* 293HT96 exposed to continuous infusion of both ceftazidime and avibactam at final concentrations of 8.2 and 1.55 mg/L, respectively (lines a and b in Figure1). The AUC_{0-24} of ceftazidime was 195 mg·h/L, and that of avibactam was 36.8 mg·h/L. (○) Colony counts of *E. cloacae* 293HT96 exposed to continuous infusion of ceftazidime at a concentration of 8.2 mg/L (AUC_{0-24} 195 mg·h/L) plus the avibactam single-dose profile. The concentration of avibactam at t = 12 hours was estimated to be 0.15 mg/L by extrapolation of the measured log10-concentration-time line at times up to 8 h. The horizontal dashed line indicates 99.9% bacterial kill from the initial bacterial number-density of the control, 1.0×10^6 CFU/mL. For reference the initial inocula for avibactam continuous infusion (squares) and avibactam single-dose (circles) were 1.7×10^6 and 3.0×10^5 CFU/mL, respectively.

Studies of Enterobacteriaceae in the hollow-fiber system showed that in the background of simulated human pharmacokinetics of a 2 g dose (30-min infusion) of ceftazidime, growth suppression for 12–24 hours could be achieved by instilling avibactam at a constant concentration of 0.5 mg/L for 4.5 hours (Study CAZ104-M2-046). This, combined with the observations in Table 12, meant that a C_T appropriate for estimating probabilities of pharmacodynamic target attainment for avibactam in combination with ceftazidime against *Enterobacteriaceae* would be ~0.5 mg/L.

In Animal Models (ceftazidime-avibactam against ceftazidime-resistant P. aeruginosa in neutropenic mouse thigh infections):
The principles of determining the appropriate pharmacodynamic index and magnitude of avibactam in restoring the activity of ceftazidime against infecting, ceftazidime-resistant, *P. aeruginosa* in animal models were as follows. First, it was necessary to establish a dose of ceftazidime monotherapy for each bacterial strain that would just allow maximal growth in the mouse model (Figure 4). The concept was to poise the ceftazidime dose-response of the system at a point at which any increase in antibacterial potency caused by inhibition of β-lactamase by avibactam would result in a fall of bacterial counts. It would then be possible, in principle, to titrate the dose of avibactam by amount and frequency in an analogous way to dose-variation and-fractionation of a monotherapy. The ceftazidime dosing was thus set to maximize the potential pharmacodynamic change caused by increasing doses of avibactam to maximize the

range of the possible response without loss of sensitivity caused by too-low a dose of ceftazidime (Figure 4).

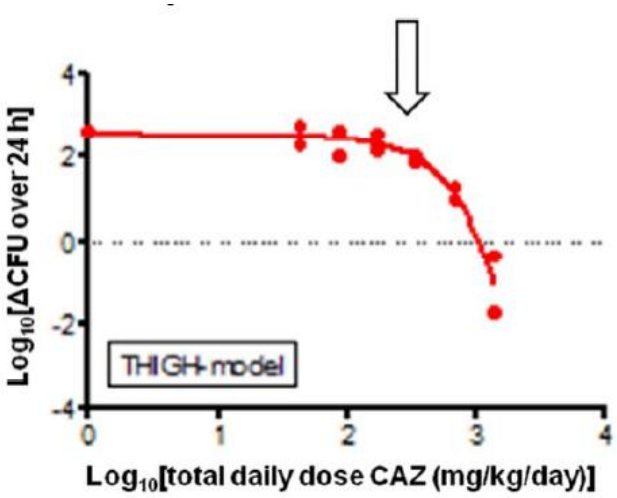


Figure 4. Ceftazidime monotherapy of *P. aeruginosa* thigh infection in neutropenic mice.
Ceftazidime was dosed 2-hourly for 24 hours to neutropenic mice infected by *P. aeruginosa* strain 7 (derepressed AmpC, no Class A or Class B β-lactamase gene detected; MIC of ceftazidime 64 mg/L; MIC of ceftazidime-avibactam 4 mg/L, tested with avibactam at fixed 4 mg/L). The dose of ceftazidime that was then selected for avibactam dose-range and dose-fractionation studies (27.2 mg/kg q2h; 326 mg/kg/day: marked by the arrow in the figure) was the highest dose of ceftazidime that still allowed the maximal 1-2-log of bacterial growth in the mouse thighs as compared to the growth observed in control animals at the start of dosing: i.e. Δ 1-2 $\log_{10}$(CFU). This meant that reductions in bacterial count towards stasis and bacterial killing, caused by superimposed dosing of avibactam added to the thus-identified ceftazidime regimen, would be a consequence of the avibactam inhibiting β-lactamase activity: thereby allowing the antibacterial pharmacology of ceftazidime to be re-exerted.

This approach resulted in dose-response curves for avibactam when it was administered in the presence of a background every 2 hours dosing of the 'poise' amount of ceftazidime determined empirically as described above. Doses of avibactam were fractionated in the background of this single 2-hourly dosing schedule of ceftazidime in order to distinguish between potential pharmacodynamic indices: fAUC, fCmax, and time. Diagnostic plots are shown in Figure 5. For the first two cases, the pharmacodynamics response was plotted as a function of AUC or C_{max} even though when eventually quantifying those indices, they might need to be expressed as a ratio against some reference concentration (analogous to AUC/MIC and C_{max}/MIC). This is because whatever that reference concentration might be, it would be a constant for every measurement of AUC and C_{max} related to every dose and the curve-fit would be unchanged if the reference concentration were set equal to any number. Thus, a dimensionless value of unity was used for convenience (i.e. AUC/1 and Cmax/1) for the initial, diagnostic, plots (Figure 5). However, in the case of time as the potential pharmacodynamic index, it was necessary to choose that reference concentration. This is because time above a particular concentration does not scale linearly with dose. That is, the curve fitting of the data to fT > (a reference concentration) would provide different fits depending on the magnitude chosen for that reference concentration. Deciding on an appropriate reference concentration was achieved by plotting the pharmacodynamics response against fT > C_T for 3 values of C_T, covering a 16-fold range: 0.25 mg/L, 1 mg/L, and 4 mg/L (Figure 5) and assessing the best fit.

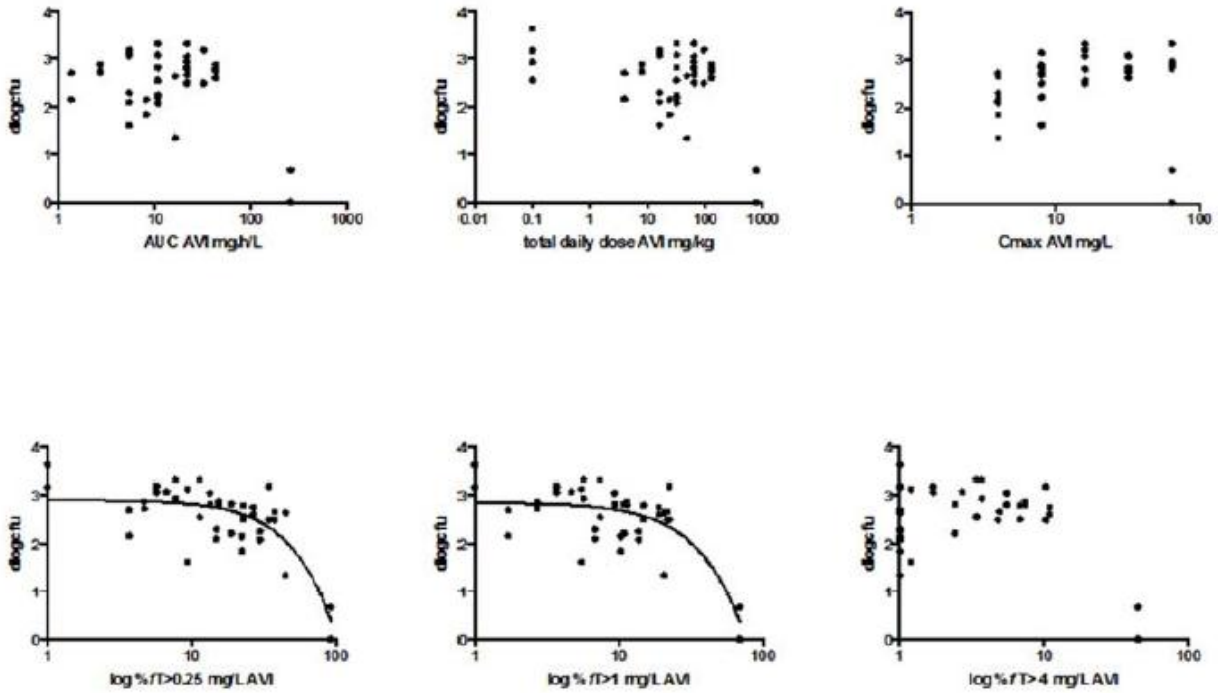


Figure 5. 'Diagnostic' plots of AUC, Cmax, and fT > reference concentration for different fractionated dose regimes of avibactam in the background of 2-hourly ceftazidime dosing against ceftazidime-resistant *P. aeruginosa* in a neutropenic mouse thigh infection model (Study CAZ-AVI-M1-66). Avibactam doses were fractionated over 24 hours in neutropenic mice infected by P. aeruginosa strain 7 (MIC of ceftazidime, 64 mg/L; MIC of ceftazidime-avibactam, 4 mg/L, tested with avibactam at fixed 4 mg/L) in the background of a regular 2-hourly dose of ceftazidime of 27.2 mg/kg.

From the diagnostic plots, the index that best fit the pharmacodynamic response data was fT > (concentration) (Figure 5). Clearly the only relationship between the pharmacodynamic effect of avibactam and its C_{max} might have been a slight trend to lower efficacy with increasing C_{max} (top right panel of Figure 5). In other words, C_{max} was not the driver of efficacy. However, AUC and fT > concentration were less easy to distinguish. The following experiment, using the neutropenic lung infection model, tested the hypothesis that fT > concentration was a more predictive avibactam index than AUC in determining bacterial killing and inhibition of growth in the presence of ceftazidime concentrations with 2 hourly dosing of 27.2 mg/kg ceftazidime. Identical daily doses of avibactam were given every 2 hours or every 8 hours and inhibition of growth and killing of *P. aeruginosa* in the lungs of neutropenic mice were monitored by counting CFU/lung (Figure 6).

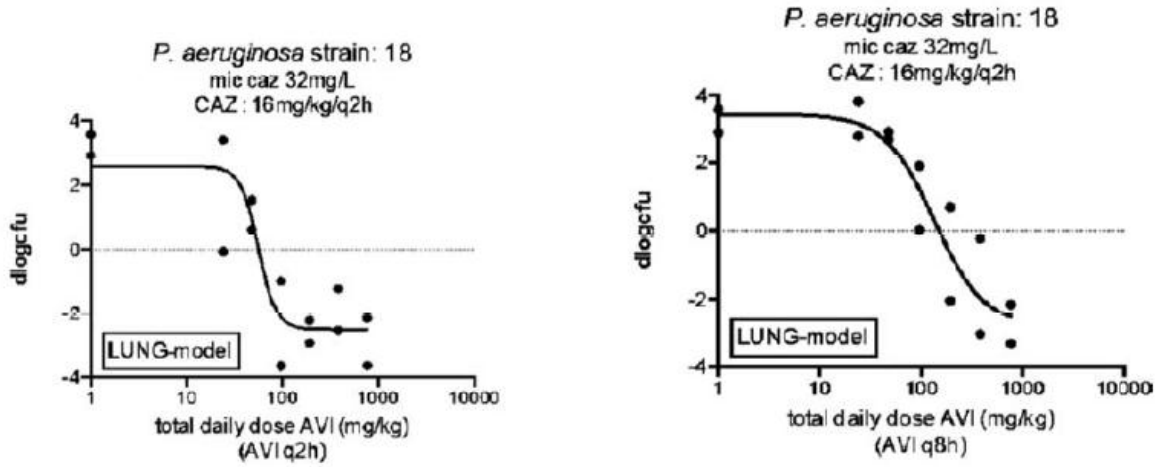


Figure 6. PK/PD of avibactam therapy when added to 2-hourly ceftazidime dosing against ceftazidime-resistant *P. aeruginosa* in a neutropenic mouse lung infection model (Study CAZ-AVI-M1-66). Avibactam was dosed q2h (left panel) or q8h (right panel) for 24 hours to neutropenic mice infected by *P. aeruginosa* strain 18 (MIC of ceftazidime, 32 mg/L; MIC of ceftazidime-avibactam, 2 mg/L, tested with avibactam at fixed 4 mg/L) in the background of a repeated 2-hourly dose of ceftazidime of 16 mg/kg. At the lowest doses of avibactam, bacterial growth was close to that in untreated control animals, whereas at the highest doses, near maximal killing occurred.

In this experiment, the avibactam AUC exposures were identical between the two schedules. However, greater fT > (reference concentration) magnitudes were obtained from 2-hourly (left panel) than from 8-hourly (right panel) dosing. For example, for a total daily dose of 96 mg/kg/day (~2 on the logarithmic horizontal axes of Figure 6), the fT > 1 mg/L from 2-hourly dosing was 32.8% of each dosing interval but for 8-hourly dosing it was only 14.1% of each dosing interval. The greater fT > (reference concentration) exposures of avibactam yielded a greater pharmacodynamic response. For example, taking bacterial stasis as an easily-readable endpoint, the total daily dose required in the 8-hourly dosing schedule was 150 mg/kg, whereas it was about 57 mg/kg/day in the case of 2-hourly dosing. Altogether, the data support that the index that best fit the pharmacodynamic response data was fT > (concentration).

In addition to two full dose-fractionation experiments, one of which is shown in Figure 5, the %fT > 1 mg/L that provided bacterial stasis was measured in co-dosing experiments (i.e. avibactam dosed simultaneously with ceftazidime q2h) with 6 strains of *P. aeruginosa*. The mean magnitude of the %fT > 1 mg/L that yielded stasis over 24 hours in those co-dosing experiments was 36.3% (± 17.8) (CAZ-AVI-M1-066). A summary of all estimated fT > 1 mg/L associated with the bacterial response of stasis in the neutropenic mouse thigh is shown in Table 13. The arithmetic mean of these 8 magnitudes was 40.2% fT > 1 mg/L for stasis. The mean magnitude associated with 1-log10 kill was 50.3%. Three isolates responded with 2-log10 kill (Table 13) at avibactam fT > 1 mg/L of 45.0-48.4%.

Table 13. Magnitudes of avibactam exposures associated with stasis and 1- and 2-log_{10} kills of *P. aeruginosa* infecting the thighs of neutropenic CD-1 female mice in the background of 2-hourly dosing of ceftazidime (Study CAZ-AVI-M1-66)

Strain	**Experiment**	**Avibactam fT > 1 mg/L yielding:**		
		Stasis	***1-log10 kill***	***2-log10 kill***
1	co-dosing	37.2%	65.7%	not reached
5	co-dosing	14.1%	32.9%	48.4%
7	AVI fractionation	30.2%		
7	co-dosing	50.4%	65.3%	not reached
11	co-dosing	29.1%	37.5%	46.8%
18	AVI fractionation	74.1%		
18	co-dosing	24.2%	33.2%	45.0%
19	co-dosing	62.5%	67.2%	not reached
Mean		40.2%	50.3%	

In Animal Models (ceftazidime-avibactam against ceftazidime-resistant P. aeruginosa in neutropenic mouse lung infections):
As in the mouse-thigh infection experiments, the PK/PD targets for the avibactam exposure index, fT > C_T 1 mg/L, that yielded different bacterial pharmacodynamic responses including stasis, 1-log, and 2-log kill was determined in the neutropenic mouse lung infection model (Table 14). The PK/PD target for stasis was 16-24% fT > 1 mg/L (mean 20.2%); although it was noted that it varied with the background exposure of ceftazidime. The PK/PD target for avibactam for a bactericidal response of 1-log_{10} kill was 18–35% (mean 24%) fT > 1 mg/L in combination with background dosing of ceftazidime. The PK/PD target for avibactam and a bactericidal response of 2-log_{10} was not observed with every *P. aeruginosa* strain tested; but of those where it did occur, the PK/PD target was 20-55% fT > 1 mg/L (mean 30.3%).

Table 14. Magnitudes of avibactam exposures associated with stasis and bacterial killing of *P. aeruginosa* in the lungs of neutropenic CD-1 female mice in the background of pharmacokinetic cycling of ceftazidime (Study CAZ-AVI-M10-066)

Strain	***Experiment***	***Avibactam fT > 1 mg/L[a] associated with:***		
		stasis	***1-log10 kill***	***2-log10 kill***
5	co-dosing	19.4%	20.6%	21.5%
7	co-dosing	21.4%	22.4%	no data
11	co-dosing	19.7%	34.9%	55.3%
11	AVI fractionation	20.9%	21.6%	22.5%
18	co-dosing	23.5%	26.7%	31.8%
18	AVI fractionation	16.1%	17.8%	20.2%
Mean		20.2%	24.0%	30.3%

[a] Times are expressed as % of the dosing interval.

Because PK/PD targets could not be identified from the exposure-response analyses of the Phase 2 studies in cIAI and cUTI, PK/PD targets based on the animal models of infection described above were used in simulations to determine probability of PK/PD target attainment for CAZ-AVI at the recommended clinical dose. From the above data, a conservative target of 50% fT>1.0 mg/mL was used as the PK/PD target for avibactam to restore the activity of ceftazidime against infecting, ceftazidime-resistant, *P. aeruginosa*.

Population PK of CAZ-AVI

Population PK analyses have been conducted for both avibactam and ceftazidime based on a pooled plasma concentration dataset from the Phase 2 cIAI study (NXL104/2002), five Phase 1 clinical pharmacology studies in healthy volunteers, and subjects with impaired renal function (CAZ-MS-01). The analysis demonstrated that the main predictors of clearance (CL) for avibactam and ceftazidime were body surface-normalized creatinine clearance (nCrCl) and CrCl, respectively, consistent with the predominant renal excretion of both compounds. In addition, cIAI was identified as a significant covariate impacting clearance and central volume of distribution of both avibactam and ceftazidime. The typical values of avibactam CL and central volume of distribution were higher in the cIAI population compared to healthy volunteers. The population PK model predicted a 34% and 59% decrease in the mean steady state AUC and C_{max} for avibactam, respectively, for Phase 2 cIAI subjects with normal renal function compared to Phase 1 subjects with normal renal function. Similarly, typical values of ceftazidime CL and central volume of distribution were higher in the cIAI population compared to healthy volunteers. The population PK model predicted a 20% and 38% decrease in the mean steady state AUC and C_{max} for ceftazidime, respectively, for Phase 2 cIAI subjects with normal renal function compared to Phase 1 subjects with normal renal function.

Probability of target attainment (PTA) analysis using Monte Carlo simulation of human PK

The population PK models for ceftazidime and avibactam were used to explore PK/PD relationships in the Phase 2 studies and to conduct simulations to evaluate the probability of joint PK/PD target attainment for ceftazidime and avibactam. The PTA analyses were used to support proposed breakpoints and to indirectly support the efficacy of CAZ-AVI against ceftazidime-nonsusceptible microorganisms.

As described above, the PK/PD targets associated with efficacy of CAZ-AVI have been shown to be %fT > MIC and %fT > C_T for ceftazidime and avibactam, respectively. The target from the nonclinical studies (i.e., 50% fT > CAZ-AVI MIC for ceftazidime and 50% fT > C_T of 1 mg/L for avibactam) were used in simulations to assess the PTA.

The population PK models for ceftazidime and avibactam were used to conduct Monte Carlo simulations to determine the probability of PK/PD target attainment to support CAZ-AVI dose selection for subjects across 6 different levels of renal function, spanning from normal renal function to ESRD. The dose regimens simulated were based on the dose adjustments by renal function for ceftazidime in the US FORTAZ label (FORTAZ® package insert, 2010), with the avibactam dose adjusted to maintain the CAZ-AVI dose ratio at 4:1 (see below for the discussion of the dose ratio of ceftazidime:avibactam). Demographic covariates and CrCL for 5000 theoretical subjects were simulated for each renal function group. Because subjects with cIAI showed lower exposures than healthy subjects and subjects with cUTI, the cIAI population was

used to simulate exposures and calculate associated target attainment. For the simulation of subjects with normal renal function, the demographics for the simulation were bootstrapped from the observed weight and CrCL values in the cIAI Phase 2 study. For the simulation of subjects in each of the reduced renal function categories, the same bootstrapped distribution of weight was chosen as a conservative assumption, while for CrCL, a uniform distribution was used within each sub-category. PK/PD target attainment was calculated as the percentage of the simulated subjects who met the PK/PD targets for both ceftazidime and avibactam simultaneously (referred to as joint PK/PD target attainment). The results for a 2-hour IV infusion are shown in Table 15, with target attainment by renal function group at the proposed dose regimen.

Table 15. Percentage of simulated patients with cIAI achieving PK/PD target (i.e., 50%*f*T > MIC for ceftazidime and 50%*f*T > 1.0 mg/L for avibactam) for different renal function groups (5000 simulated subjects per group) with CAZ-AVI given as a 2-hour IV infusion.

Renal function	***Proposed Dose regimen***	***% of simulated patients achieving PK/PD target***
CAZ-AVI MIC=4 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	98.9
MILD	2000 mg CAZ + 500 mg AVI, q8h	99.9
MOD	1000 mg CAZ + 250 mg AVI, q12h	98.9
SEV1	1000 mg CAZ + 250 mg AVI, q24h	97.8
SEV2	500 mg CAZ + 125 mg AVI, q24h	100
ESRD	500 mg CAZ + 125 mg AVI, q48h	100
CAZ-AVI MIC=8 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	98.1
MILD	2000 mg CAZ + 500 mg AVI, q8h	99.9
MOD	1000 mg CAZ + 250 mg AVI, q12h	95.7
SEV1	1000 mg CAZ + 250 mg AVI, q24h	85.9
SEV2	500 mg CAZ + 125 mg AVI, q24h	94.4
ESRD	500 mg CAZ + 125 mg AVI, q48h	99.9
CAZ-AVI MIC=16 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	50.8
MILD	2000 mg CAZ + 500 mg AVI, q8h	93.8
MOD	1000 mg CAZ + 250 mg AVI, q12h	35.2
SEV1	1000 mg CAZ + 250 mg AVI, q24h	21.8
SEV2	500 mg CAZ + 125 mg AVI, q24h	40.8
ESRD	500 mg CAZ + 125 mg AVI, q48h	84.7
CAZ-AVI MIC=32 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	1.3
MILD	2000 mg CAZ + 500 mg AVI, q8h	27.5
MOD	1000 mg CAZ + 250 mg AVI, q12h	0.4
SEV1	1000 mg CAZ + 250 mg AVI, q24h	0.3
SEV2	500 mg CAZ + 125 mg AVI, q24h	2.3
ESRD	500 mg CAZ + 125 mg AVI, q48h	36.8

Figure 7 shows the percentage of simulated cIAI subjects that achieve joint PK/PD targets overlaid on histograms of MIC distributions for *Enterobacteriaceae* and *P. aeruginosa*. These results demonstrate that the proposed CAZ-AVI dose of 2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h infused over 2 h will provide adequate exposures to cover the most likely pathogens to be encountered among serious infections in the clinical setting based on analysis of extensive surveillance data.

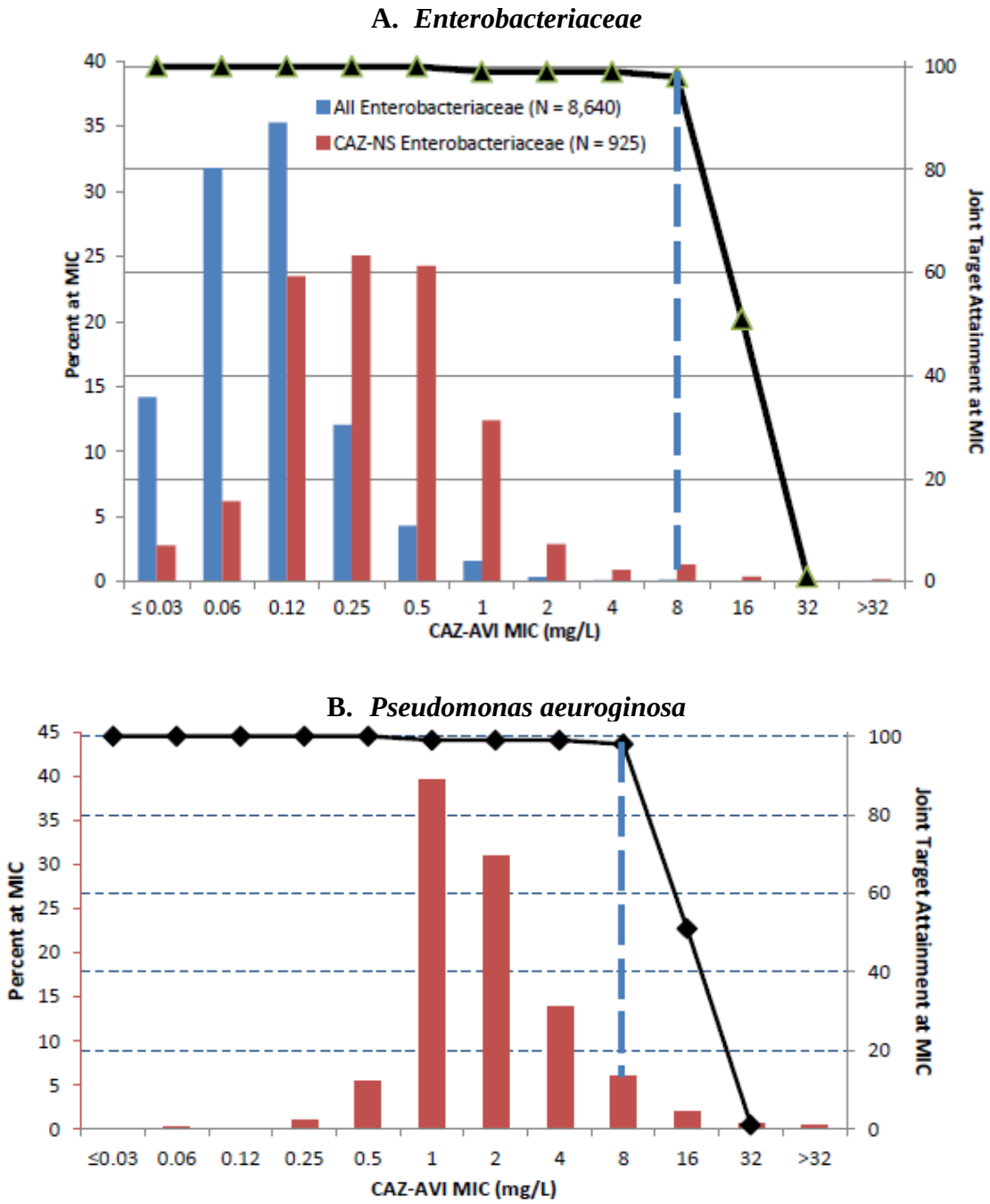


Figure 7. Percentage of simulated cIAI patients achieving joint PK/PD target attainment following IV administration of proposed CAZ-AVI dose overlaid on a histogram of MIC

distributions for *Enterobacteriaceae* (A) and *Pseudomonas aeruginosa* (B). The MIC distributions were based on surveillance data.

Simulations were also conducted for cUTI subjects (data are not presented) with the proposed dose. Simulated exposures were higher in cUTI subjects than cIAI, based on the population-related differences in population PK model estimates. Although this increased some of the joint PTA results above 90% for additional renal function categories at 16 mg/L, the combined results for joint PTA for cUTI across all renal categories supported a PK/PD breakpoint of 8 mg/L.

Additional Animal Efficacy Studies using Human-simulated Pharmacokinetics

A series of studies were conducted using dosing regimens to achieve free drug concentration-time profiles in animals that approximate those in humans given 2 g ceftazidime q8h (2-h infusion), with or without avibactam at 0.5 g q8h (2-h infusion). The results of these studies, at least indirectly, support the PK/PD target attainment analyses that led to selection of the proposed CAZ-AVI dose regimen of 2.5 g q8h as a 2-h infusion. The target concentration-time courses shown in Figure 8 were tested experimentally in several murine studies.

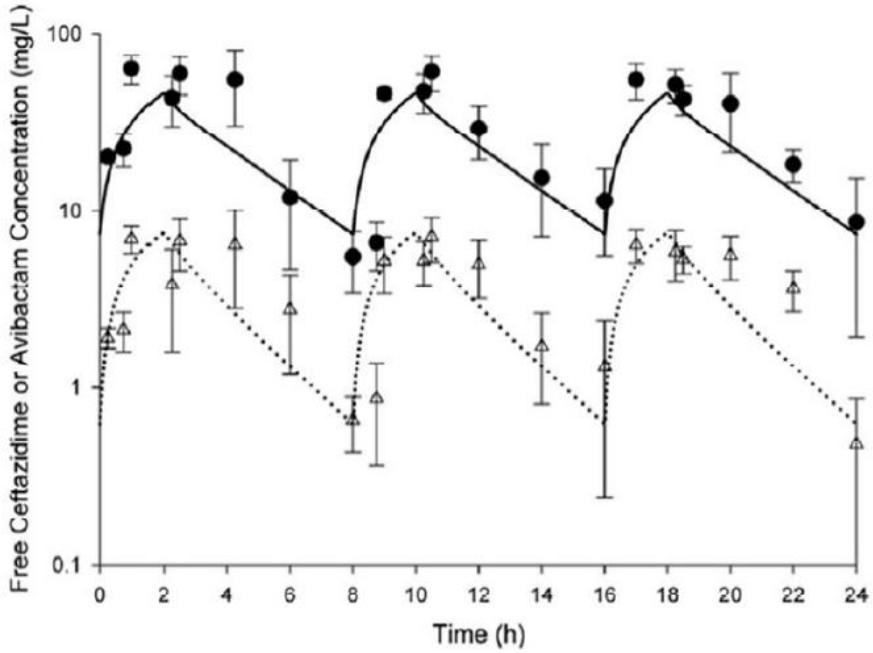


Figure 8. Target pharmacokinetic profiles of ceftazidime and avibactam in experimental studies of bacterial responses compared to approximated human exposures. Free concentration-time profiles for 2-h infusions of ceftazidime (2 g) and avibactam (500 mg) in the Monte Carlo simulated median patient (solid line and dotted line, respectively) and experimental measurements of free concentrations of ceftazidime-avibactam from mice in the human simulated exposure studies (circles and triangles, respectively). Murine data show mean values ± 1 standard deviation.

Murine Neutropenic Thigh Infection Model:

The efficacy of CAZ-AVI in the murine thigh infection model against 27 isolates of *P. aeruginosa* with ceftazidime MICs ranging from 8 to 128 mg/L and CAZ-AVI MICs ranging from 4 to 32 mg/L has been evaluated. The free drug-concentration time profile seen in humans given 2 g ceftazidime q8h (2-h infusion), with or without avibactam at 0.5 g q8h (2-h infusion)

was studied (see Figure 8). The animals were treated with ceftazidime or CAZ-AVI 2 h post infection and the change in bacterial burden in the thigh was determined after 24 h and compared with the 0-h controls.

The human simulated regimen produced predictable efficacy (based on MIC), with bacterial killing (0.7- to > 3-log reductions in bacterial counts) against 16 of 17 isolates with CAZ-AVI MICs that were ≤ 8 mg/L and 5 of 8 isolates with CAZ-AVI MICs of 16 mg/L (Figure 9). Two isolates with CAZ-AVI MIC values of 32 mg/L were also studied. One isolate responded with a 1-$\log_{10}$ reduction in titer and the other resulted in net stasis. After the 24-h treatment period with CAZ-AVI, no bacterial colonies were observed from thigh homogenates plated on drug-containing plates, suggesting that there was no resistance development.

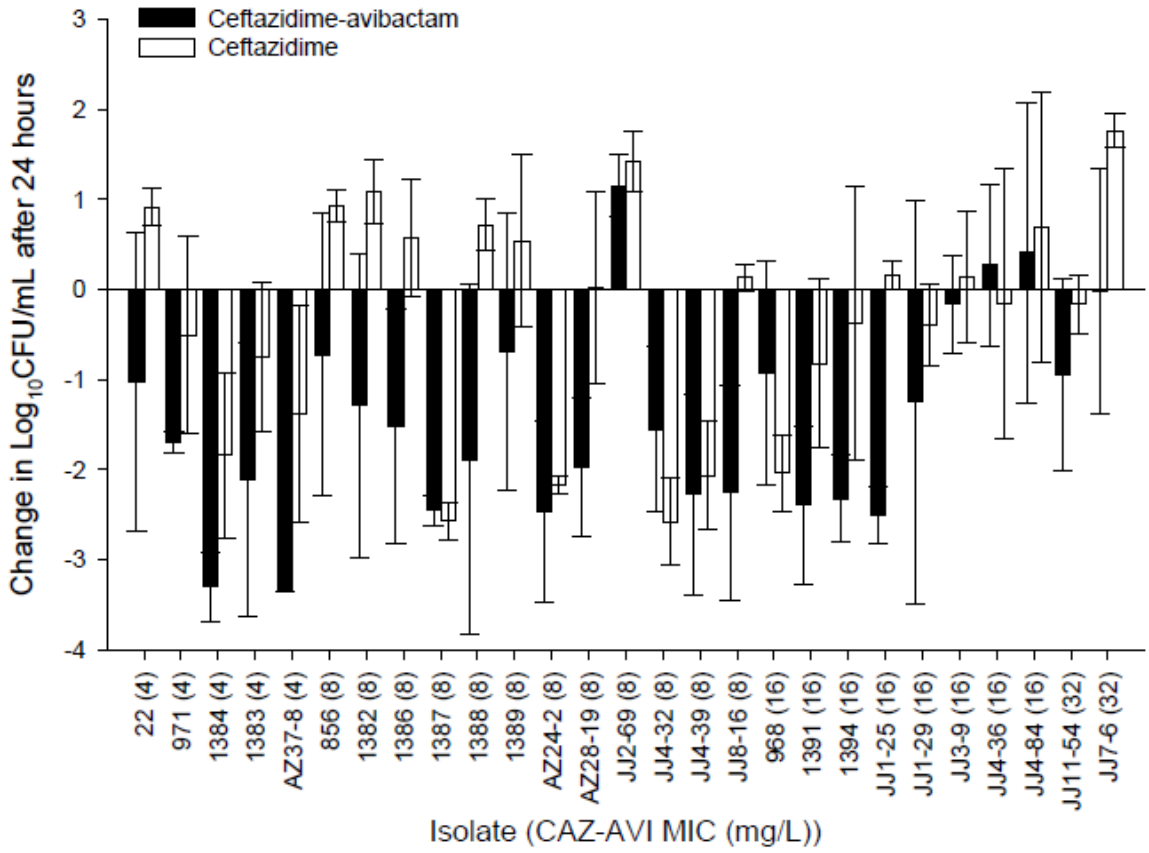


Figure 9. Comparative efficacies of simulated human pharmacokinetics of ceftazidime-avibactam and ceftazidime alone against a distribution of *P. aeruginosa* in the thighs of neutropenic mice (Study CAZ104-M1-002). CAZ-AVI MIC = MIC of ceftazidime-avibactam, tested with a fixed concentration of avibactam of 4 mg/L. Mice were rendered neutropenic by pre-treatment with cyclophosphamide. Three days prior to inoculation, mice were given a single 5 mg/kg intraperitoneal injection of uranyl nitrate, causing renal impairment to slow drug clearance. Each thigh was inoculated intramuscularly with a 0.1 mL solution containing approximately 10^7 CFU/mL of the test isolate (i.e., inocula of ca. 1×10^6 CFU). For each of the 27 *P. aeruginosa* isolates, groups of 3 mice were administered human simulated regimens of ceftazidime or ceftazidime-avibactam beginning 2 hours after inoculation. Animals were sacrificed at 24 hours after the initiation of therapy, and CFU was counted by plating serial dilutions of homogenized thigh suspensions. A group of 3 infected, untreated mice were harvested at the initiation of dosing and served as 0 hour controls. Efficacy was calculated as the change in log10 (bacterial CFU/thigh) obtained for treated mice after 24 hours from the starting densities observed in 0 hour control animals. MIC values of ceftazidime-avibactam are shown in brackets by the

name of each isolate. MIC values of ceftazidime alone were > 32 mg/L except for two isolates: #856 (8 mg/L) and #971 (16 mg/L). Error bars represent mean ± standard deviations.

In a second study by the same investigators, the efficacy of CAZ-AVI against *Enterobacteriaceae* with MIC values ≥ 8 mg/L was evaluated (Figure 10). For 2 of the isolates, the β-lactamase genotype was known by genomic sequencing (*K. pneumoniae* KP 496 blaKPC-3, blaSHV-12, blaTEM-1 truncated blaOXA-9; and *Providencia stuartii* PS 58 blaACC-4, blaTEM-1). Additional isolates were added against which the CAZ-AVI MIC was ≥128 mg/L but for which the genotype was unknown. The simulated human exposures of CAZ-AVI 2.5 g q8h (2-h infusion) resulted in decreases in CFU against 13 of 14 Enterobacteriaceae with CAZ-AVI MICs ≤ 16 mg/L. The remaining isolate was an *E. cloacae* (MIC ceftazidime > 128 mg/L; MIC CAZ-AVI 8 mg/L), with a static response to CAZ-AVI. Variable activity was noted at CAZ-AVI MICs of 32 mg/L and efficacy, which was unexpected given 0% fT > MIC, was observed against isolates with CAZ-AVI MIC values ≥ 128 mg/L.

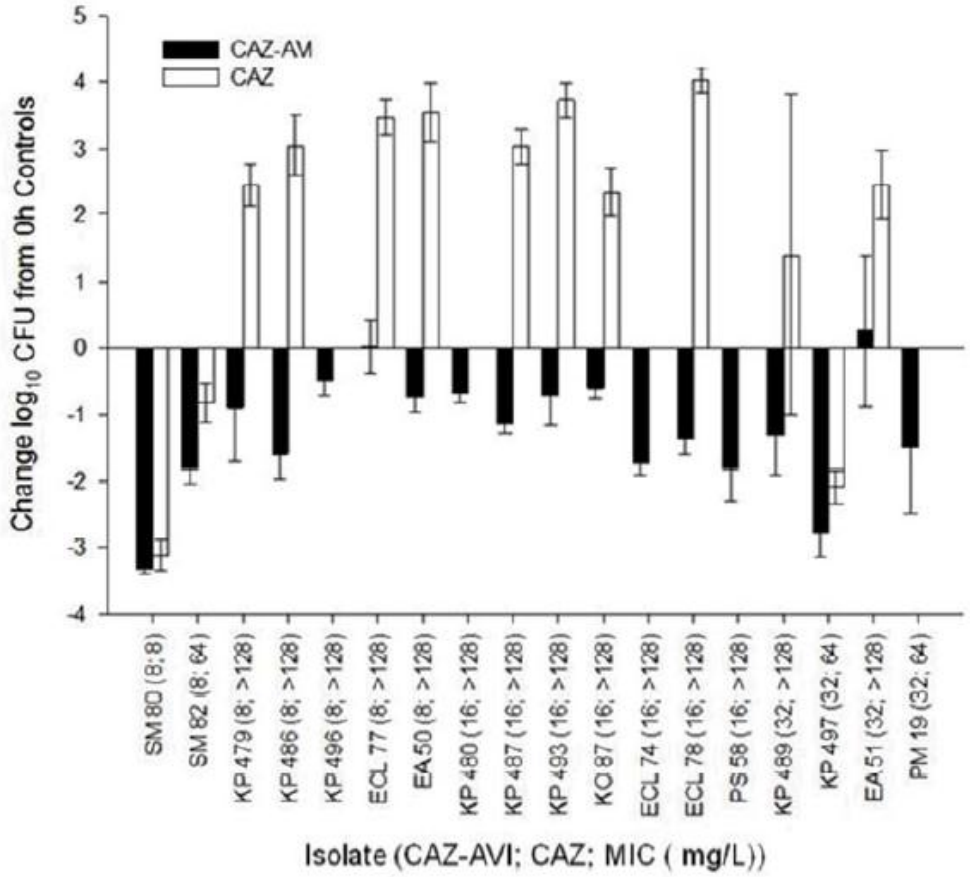


Figure 10. Efficacy of human simulated pharmacokinetics of ceftazidime plus avibactam and ceftazidime alone against *Enterobacteriaceae* (ceftazidime-avibactam MIC 8–32 mg/L) in the neutropenic murine thigh infection model (Study CAZ-AVI-M1-067). SM = *Serratia marcescens*; KP = *Klebsiella pneumoniae*; ECL = *Enterobacter cloacae*; EA = *Enterobacter aerogenes*; KO = *Klebsiella oxytoca*; PS = *Providencia stuartii*; PM = *Proteus mirabilis*. MIC values were measured using a fixed concentration of avibactam of 4 mg/L. Mice were rendered neutropenic by pre-treatment with cyclophosphamide. Three days prior to inoculation, mice were given a single 5 mg/kg intraperitoneal injection of uranyl nitrate, causing renal impairment to slow drug clearance. Each thigh was inoculated intramuscularly with a 0.1 mL solution containing approximately 10^7 CFU/mL of the test isolate (i.e., inocula of approximately 1×10^6 CFU). For each of the isolates of *Enterobacteriaceae*, groups of 6 mice were administered human simulated regimens of ceftazidime or ceftazidime-

avibactam, or saline at the same injection times, beginning 2 hours after inoculation. Ceftazidime alone was not studied against isolates KP 496, KP 480, ECL 74, PS 58, or PM 19. Animals were sacrificed at 24 hours after the initiation of therapy, and CFU counted by plating serial dilutions of homogenized thigh suspensions. A group of 3 infected, untreated mice were harvested at the initiation of dosing and served as 0 hour controls. Efficacy was calculated as the change in log10 (bacterial CFU/thigh) obtained for treated mice after 24 hours from the starting densities observed in 0 hour control animals. MIC values of ceftazidime-avibactam and ceftazidime are shown in brackets by the name of each isolate. Error bars represents mean ± standard deviations.

Murine Pneumonia Model:

The effect of simulated human CAZ-AVI PK on 28 *P. aeruginosa* isolates in a neutropenic mouse lung infection model was also studied (Figure 11). CAZ-AVI demonstrated 1- to 4–log reductions in bacterial titers over 24 h against 26 of 27 *P. aeruginosa* isolates that tested with MIC values of ≤ 32 mg/L. The 1 exception was an isolate with a CAZ-AVI MIC of 16 mg/L. Activity was also not observed against the 1 isolate with a CAZ-AVI MIC of 64 mg/L. Similarly, simulated human PK of ceftazidime alone resulted in 0.5- to 2-log reductions in bacterial titers over 24 h against isolates that tested with ceftazidime MICs of 32 or 64 mg/L. The median PK profile used in these experiments provided 34% fT > 32 mg/L, and 6% fT > 64 mg/L. The approximated median human exposure of ceftazidime was less effective against isolates for which the ceftazidime MIC was 128 mg/L where 1 of 3 isolates responded with an approximately 1.5 -log reduction in count, and the other 2 responded with stasis.

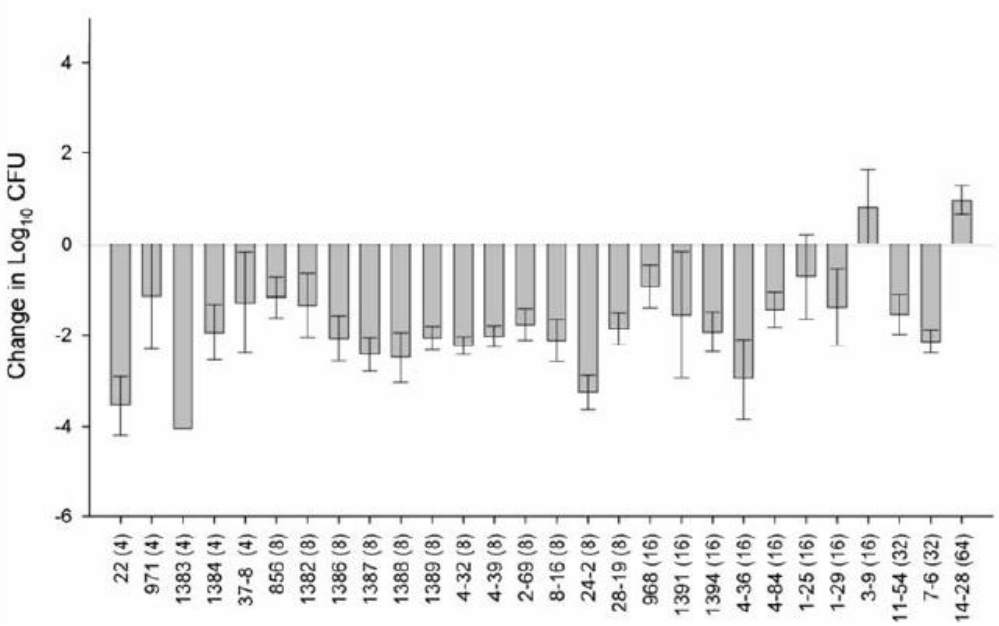


Figure 11. Efficacy of human simulated pharmacokinetics of ceftazidime plus avibactam against *P. aeruginosa* in the neutropenic murine lung infection model (Study CAZ-AVI-M1-062). Mice were rendered neutropenic by pre-treatment with cyclophosphamide. Three days prior to inoculation, mice were given a single 5 mg/kg intraperitoneal injection of uranyl nitrate, causing renal impairment to slow drug clearance. Anesthetized mice were inoculated with 0.05 mL of 10^7 CFU/mL suspension of the infecting *P. aeruginosa* isolate (MIC values of ceftazidime-avibactam, avibactam at fixed 4 mg/L, are shown in brackets by the isolate number). The inoculum was administered into the mouths of the mice while blocking their nares to induce aspiration. Therapy commenced 2 hours after inoculation. Animals were sacrificed 24 hours after the initiation of therapy, and CFU counted by plating serial dilutions of homogenized lung suspensions. A group of 6 infected, untreated mice were harvested at the initiation of dosing and served as 0 hour controls. Efficacy was calculated as the change in the

24 hour $\log_{10}$ (bacterial CFU/lung) obtained for treated mice compared with the starting densities observed in 0 hour control animals. Bars represent mean ± SD.

Evaluation of the dose ratio of ceftazidime:avibactam

Results of the following murine infection model studies support that the dose ratio of avibactam to ceftazidime in the final product (4:1, w:w) is appropriate to restore the activity of ceftazidime against ceftazidime-resistant strains. Percent survival as a function of the dose of ceftazidime with or without avibactam in varied ratios is plotted in Figure 12. Against the KPC-2 producer *K. pneumoniae* VA-361, the 4:1 and 8:1 (ceftazidime:avibactam) ratios yielded similar survival curves. Against the other KPC-2 producing isolate, *K. pneumonia* VA-406, the survival curves generated by the 4:1 and the 2:1 (ceftazidime:avibactam w/w) ratios were similar.

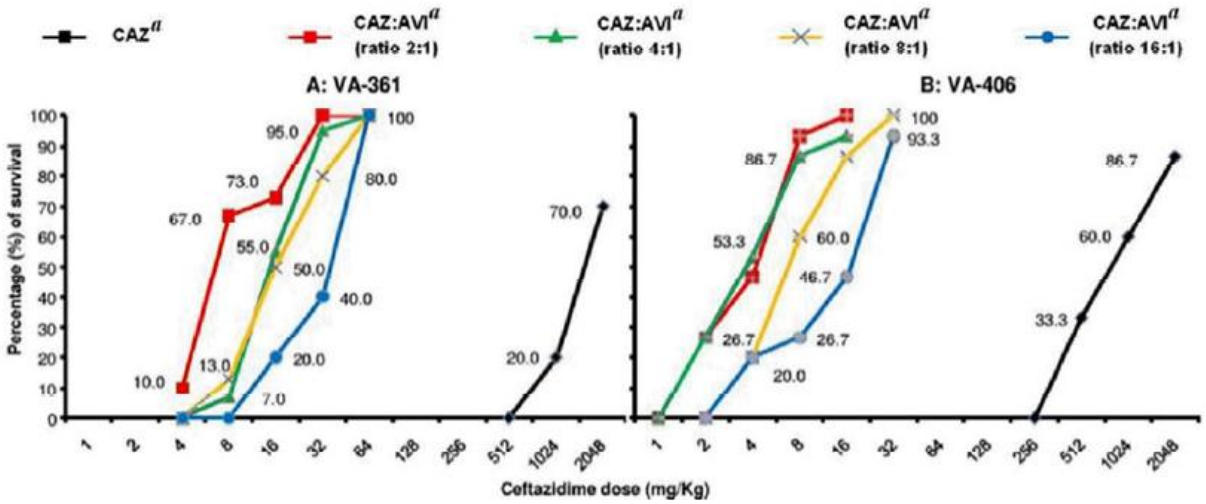


Figure 12. Survival curves for mice treated with ceftazidime with and without avibactam in the murine septicemia model due to KPC-producing *K. pneumoniae*

The antibacterial activity of the combination of ceftazidime-avibactam (ceftazidime:avibactam 4:1 and 2:1, w/w) was also compared to the activities of ceftazidime alone, ceftazidime-clavulanate (4:1 and 2:1, w/w), and imipenem in a *K. pneumonia* neutropenic mouse pneumonia model (Table 16). The mean $\log_{10}$ [bacterial count (CFU/g lung tissue)] were not substantially different between (ceftazidime:avibactam 4:1, w/w) and (ceftazidime avibactam 2:1, w/w) groups, together with the results of the above study (i.e., Figure 12), indicating that the dose ratio of ceftazidime:avibactam in the final product (4:1,w/w) is appropriate to restore the activity of ceftazidime against ceftazidime-resistant strains.

Table 16. Efficacy of ceftazidime-avibactam against ceftazidime-resistant β-lactamase-producing *K. pneumoniae* in a neutropenic mouse pneumonia model (Study CAZ104-M1-004-NXL104-AP0004).

Time post-initiation of therapy	*MIC (mg/L)*			*Mean log_{10} [bacterial count (CFU/g lung tissue)]*				
	CAZ[a]	*CAZ-AVI*[b] *(4:1)*	*IPM*[c]	*Control*[d]	*CAZ-150*[a]	*CAZ-AVI-150*[b]		*IPM*[c]
						2:1	*4:1*	
***K. pneumoniae* 283KB4 (DHA-2)**[a]								
	> 256	4	1					
0 h				11.2				
24 h				11.4	10.2	7.9	8.6	10.0
48 h				-	7.9	5.7	5.6	6.1
***K. pneumoniae* 283KB5 (LAT-4, SHV-11)**[a]								
	32	1	1					
0 h				11.2				
24 h				12.6	11.4	6.2	5.4	7.8
48 h				-	11.9	4.6	4.6	4.4

[a]: CAZ = ceftazidime dosed at 150 mg/kg q8h
[b]: CAZ-AVI = ceftazidime-avibactam. The ceftazidime-avibactam MIC was measured by dilution of the compounds in a fixed 4:1 ratio: because these experiments were performed before the susceptibility testing standard was established of diluting ceftazidime while maintaining the concentration of avibactam constant at 4 mg/L. CAZ-AVI-150 = ceftazidime-avibactam dosed at 150+75 mg/kg q8h (labeled 2:1) or at 150+37.5 mg/kg (labeled 4:1).
[c]: IPM = imipenem; dosed at 150 mg/kg q8h.
[d]: Dosed with saline.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

There were no clinically significant adverse events observed in the clinical studies. Thus, formal exposure-response relationships for safety were not conducted for CAZ-AVI. In the Phase 2 cIAI and cUTI studies, the overall incidence of treatment-emergent adverse events (TEAEs), severe adverse events (SAEs), discontinuations of study drug due to TEAEs, and deaths were similar between treatment groups (Table 17). In the cIAI study, 2.5 g was given as 30-minute infusion, whereas in the cUTI study, a 0.625 g dose was given as 30-minute infusion. There appear to be no substantial differences in adverse event rates (except death) between the cIAI patient population who received a higher dose and the cUTI patient population who received a lower dose, indirectly indicating that there may be no substantial exposure-response relationship for safety of CAZ-AVI. It should be noted that the cIAI patient population is a more severely ill population compared to the cUTI patient population and metronidazole was used together with CAZ-AVI in the cIAI study.

Table 17. Summary of adverse events by treatment group, Phase 2 studies — safety Population

	cIAI (NXL104/2002)		cUTI (NXL104/2001)	
Subjects with:	**CAZ-AVI +MTZ (N=101) n (%)**	**Meropenem (N=102) n (%)**	**CAZ-AVI (N=68) n (%)**	**Imipenem (N=67) n (%)**
Any TEAE	65 (64.4)	59 (57.8)	46 (67.6)	51 (76.1)
Any SAE	9 (8.9)	11 (10.8)	6 (8.8)	2 (3.0)
Discontinuation of study drug due to	5 (5.0)	3 (2.9)	2 (2.9)	0
Death	3 (3.0)	2 (2.0)	0	1 (1.5)

MTZ = metronidazole

2.2.4.3. Does this drug prolong the QT or QTc interval?

The effect of avibactam on the QT/QTc interval was evaluated pre-clinically and showed minimal potential for QT/QTc prolongation. In addition, a Phase 1 study (Study D4280C00007) was conducted to evaluate the potential effect of CAZ-AVI and CXL on cardiac repolarization as assessed by the QT/QTc interval. In Study D4280C00007, a supratherapeutic dose of avibactam (2000 mg) was investigated for QT effects when given in combination with a supratherapeutic dose of ceftazidime (3000 mg) as a single 30-minute infusion and with a supratherapeutic dose of ceftaroline fosamil (1500 mg) as a single 1-hour infusion. A single dose of oral moxifloxacin (400 mg) was used as the positive control.

Neither drug combination with avibactam showed a potential to prolong the QT/QTc interval in this thorough QTc study. In the primary comparison of QTcF for both Treatment A (avibactam 2000 mg/ceftaroline fosamil 1500 mg) and Treatment B (avibactam 2000 mg/ceftazidime 3000 mg) versus placebo, the upper bound of the 2-sided 90% CI did not exceed 10 ms at any time point post-dose. See the Interdisciplinary Review Team's review for the detailed results of Study D4280C00007.

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration response, and are there any unresolved dosing or administration issues?

It should be noted that the exact proposed dose and infusion time has not been evaluated in completed Phase 2 studies. In the cUTI study, a 0.625 g dose was given as 30-minute infusion. In the cIAI study, 2.5 g was given as 30-minute infusion. Additional PTA analyses showed that (a) 0.625 g CAZ-AVI q8h as a 30-minute infusion as was studied in the Phase 2 study in cUTI patients yielded insufficient target attainment in plasma for CAZ-AVI MICs up to 8 mg/L and (b) increasing the infusion time to 2 hr yielded a probability of joint target attainment of 96%. Thus, the PTA analyses supports the selection of 2.5 g CAZ-AVI q8h as a 2-hr infusion for the proposed cIAI and cUTI indications, providing adequate exposures to cover the most likely pathogens (up to 8 mg/L of CAZ-AVI MIC). In ongoing Phase 3 studies in patients with cIAI and cUTI, the proposed dose 2.5 g 2 hour infusion is being evaluated.

The proposed dosing regimen of CAZ-AVI appears to be appropriate for up to 8 µg/mL of CAZ-AVI MIC (i.e., measured using a fixed concentration of avibactam of 4 mg/L) based on the probability of target attainment (see section **2.2.4.1**) and the results of Phase 2 studies. However, the originally proposed dosing regimen for patients with renal impairments should be revised because (a) the ongoing Phase 3 cIAI study showed a lower clinical cure rate in patients with moderate (CrCL 31-50 mL/min) renal impairment who received the originally proposed dosing regimen and (b) the originally proposed dosing regimens are predicted to result in substantially lower exposure of ceftazidime and avibactam in moderate and severe renal impair patients compared with patients with normal renal function. See section **2.3** Renal Impairment for further details.

2.2.5. What are the PK characteristics of the drug and its major metabolite?

Ceftazidime is an approved product with a long clinical history, and data on the basic PK properties of ceftazidime are cited from the approved drug label (FORTAZ® US Prescribing Information) and the literature, where appropriate. Ceftazidime PK data are available from 7 of the Phase 1 CAZ-AVI studies and the 2 Phase 2 CAZ-AVI studies in which ceftazidime was administered in combination with avibactam. A limited number of in vitro CYP induction and transporter studies also were performed with ceftazidime.

2.2.5.1. What are the single and multiple dose PK parameters?

The mean PK parameters for ceftazidime and avibactam in healthy adult male subjects with normal renal function after single and multiple 2-hour IV infusions of AVICAZ 2.5 g (2 g ceftazidime and 0.5 g avibactam) administered every 8 hours are summarized in Table 18.

Table 18. Pharmacokinetic parameters (Geometric mean [%CV]) of ceftazidime and avibactam following administration of CAZ-AVI 2.5 g (2 g ceftazidime and 0.5 g avibactam) in healthy adult male subjects (Study D4280C00011)

	Ceftazidime		Avibactam	
Parameter	**Single AVICAZ 2.5 g[a] Dose Administered as a 2-hour Infusion (n = 16)**	**Multiple AVICAZ 2.5 g[a] Doses Administered q8h as 2-hour Infusions for 11 Days (n = 16)**	**Single AVICAZ 2.5 g[a] Dose Administered as a 2-hour Infusion (n = 16)**	**Multiple AVICAZ 2.5 g[a] Doses Administered q8h as 2-hour Infusions for 11 Days (n = 16)**
C_{max} (mg/L)	88.1 (14)	90.4 (16)	15.2 (14)	14.6 (17)
AUC (mg·h/L)[b]	289 (15)[c]	291 (15)	42.1 (16)[d]	38.2 (19)
$T_{1/2}$ (h)	3.27 (33)[c]	2.76 (7)	2.22 (31)[d]	2.71 (25)
CL (L/h)	6.93 (15)[c]	6.86 (15)	11.9 (16)[d]	13.1 (19)
V_{ss} (L)	18.1 (20)[c]	17.0 (16)	23.2 (23)[d]	22.2 (18)

[a]: 2 g ceftazidime + 0.5g avibactam.
[b]: AUC_{0-inf} reported for single dose administration; AUC_{0-tau} reported for multiple dose administration.
[c]: n = 15. [d]: n = 13.

2.2.5.2. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

No CAZ-AVI PK studies with intensive plasma sampling were conducted in patients. The results of the population PK analyses including sparse plasma sampling in patients with cIAI and cUTI were used to evaluate whether the PK of ceftazidime and avibactam were comparable between healthy volunteers and patients.

Ceftazidime
The Phase 2 patient population (cIAI and cUTI) was identified as a significant covariate, independent of any demographic differences (age, weight, gender, and CrCL) between the respective Phase 2 study populations and the Phase 1 study population. Increased CL was associated with the cIAI population: cIAI status increased clearance by 54%. For ceftazidime, increased V_1 was associated with the cIAI population as well as the cUTI population. Specifically, cIAI status increased V_1 by 173%, and cUTI status increased V_1 by 71%, relative to healthy subjects of similar weight.

Avibactam
The cIAI Phase 2 patient population was identified as a significant covariate, independent of any demographic differences (e.g., age, weight, gender, CrCL) between the respective Phase 2 study population and the Phase 1 study population. Specifically, cIAI status increased clearance by 40% and increased V_1 by 152% for avibactam. Both of these effects of the cIAI population in the avibactam population PK model would lead to reductions in exposure for patients with cIAI relative to healthy subjects of similar weight and renal function. In contrast, patients with cUTI showed no clinically meaningful difference in estimates of CL, but a 72% increase in V_1 as compared to healthy subjects of similar weight.

2.2.5.3. What are the characteristics of drug absorption?

Not Applicable for IV solution.

2.2.5.4. What are the characteristics of drug distribution?

The volume of distribution for ceftazidime has been reported to be from 15 to 20 L. The V_{ss} was determined in several of the studies in the CAZ-AVI program, and the values ranged from 17 to 28 L.

For avibactam, the mean V_{ss} in healthy subjects ranged from 15.2 to 24.4 L following IV infusion, suggesting that the distribution of avibactam approximates the volume of extracellular fluid.

Ceftazidime binding to human plasma protein is low and ranges from 5% to 22.8% bound. A conservative estimate of 85% was used for ceftazidime unbound fraction in plasma to calculate free drug concentrations in the population PK modeling and simulations.

In vitro plasma protein binding of avibactam, determined by ultrafiltration, was low at less than 22.1% bound across humans, mice, dogs, rabbits, and rats (Study A051132). Binding was found to be concentration dependent in animal plasma (0.25 to 2500 μg/mL), but not in human plasma (0.5 to 50 μg/mL). Avibactam was 5.7% to 8.2% bound to human plasma proteins. An estimate of 91.8% to 92% was used for avibactam unbound fraction in plasma to calculate free drug concentrations in the population PK modeling and simulations.

One study (Study D4280C00009) was performed in healthy male subjects where the concentration of ceftazidime and avibactam in bronchial ELF and plasma were compared. Following IV administration of 2000 mg ceftazidime + 500 mg avibactam as a 2-hour infusion q8h for 3 days, the $C_{max,ss}$ and $AUC_{0-\tau}$ values of ceftazidime, based on total drug concentrations, in ELF were approximately 26% and 31% of the plasma C_{max} and $AUC_{0-\tau}$, respectively. The C_{max} and $AUC_{0-\tau}$ values of avibactam, based on total drug concentrations, in ELF were approximately 35% of the plasma C_{max} and $AUC_{0-\tau}$. This indicates that both avibactam and ceftazidime distribute into ELF. A graphical comparison of drug concentration-time profiles indicated that the elimination patterns were similar between ELF and plasma for each drug (Figure 13). It should be noted that ceftazidime and avibactam were also detected in lung ELF of mice (Studies NXL104/PK0009, CAZ-AVI-M1-065, and CAZ-AVI-M1-062) at exposures lower than plasma (26.8% and 24.0% for ceftazidime and avibactam, respectively).

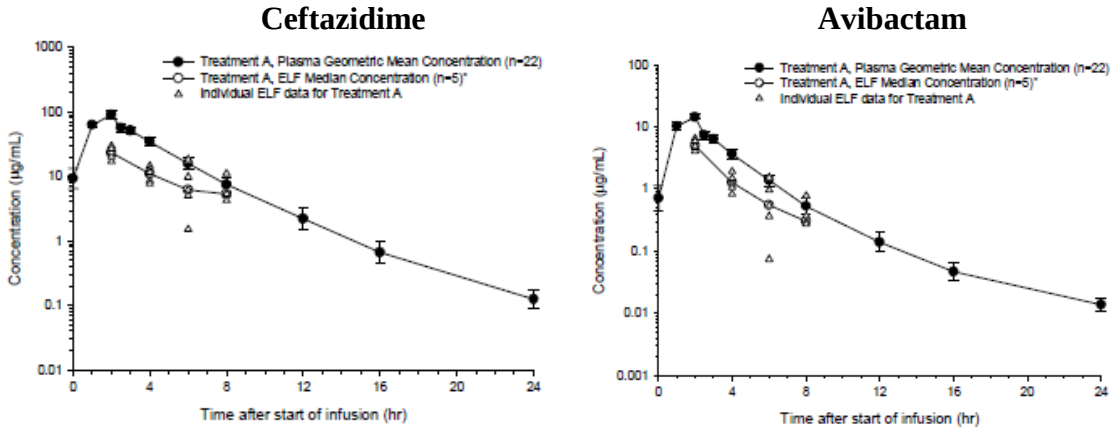


Figure 13. Plasma (geometric mean±SD) and ELF (median and individual values) concentration-time profiles of ceftazidime and avibactam following IV administration of 2000 mg ceftazidime + 500 mg avibactam as a 2-hour infusion (Study D4280C00009)

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study for ceftazidime was conducted.

Study D4280C00008 demonstrated that, following IV administration of a 500-mg dose of [^{14}C]-avibactam, an average of 97.22% (range 95.57% to 98.26%) of administered radioactivity was recovered during the study, with 97.02% (range 95.34% to 98.08%) from the urine and 0.20% (range 0.17% to 0.23%) from the feces, indicating negligible excretion via the bile. Over 95% of the administered radioactivity was recovered from urine within 12 hours of dosing.

Unchanged avibactam was the major drug-related component in human plasma and urine following dosing with [^{14}C]-avibactam. In human urine, avibactam accounted for 90% of the excreted radioactivity over 24 hours, and decarbonylated avibactam (M1) accounted for approximately 7% (Study Avibactam KMX001). M1 was not identified in human plasma but was also found in the dosing solution, suggesting that it may result from non-enzymatic processes.

2.2.5.6. What are the characteristics of drug metabolism?

Ceftazidime is not metabolized by CYP enzymes and is excreted almost entirely as unchanged drug via the kidneys (Fortaz® US Prescribing Information).

In vitro, avibactam was metabolically stable in mouse, rabbit, dog, and human liver microsomes (Studies PR6633/CC2109 and A051131). No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes), and hence, no enzyme responsible for metabolism could be identified (Studies NXL104 KMN011 and NXL104 KMX012). Unchanged avibactam was the major drug-related component in both human plasma and urine (Studies D4280C00008 and Avibactam KMX001). Two minor degradation products that are likely formed due to sample processing were also observed.

Avibactam showed no significant inhibition of CYP enzymes or UGT1A1 (Studies PR6634/CC2108, ADME-AZS-Wave3-130910, 300205, and 301113129), and avibactam and ceftazidime showed no *in vitro* CYP induction potential within the clinically relevant exposure range (Studies 100236 and 301110555).

2.2.5.7. What are the characteristics of drug excretion?

Ceftazidime is excreted almost entirely as unchanged drug via the kidneys (Fortaz® US Prescribing Information).

Neither avibactam nor ceftazidime was found to be an inhibitor of the major hepatic and renal transporters evaluated in vitro (Study 9316). Avibactam was not a substrate of MDR1, BCRP, MRP4, or OCT2 but was a substrate of human OAT1 and OAT3 kidney. Probenecid inhibits 55% to 70% of this uptake by OAT1 and OAT3.

In studies for which the amount of avibactam excreted in urine was measured (Studies NXL104-1001, NXL104/1003, NXL104/1004, D4280C00008, D4280C00011, D4280C00012, CXL-PK-01, CXL-PK-03, and CXL-PK-06), it was determined that approximately 76% to >100% of the administered dose was recovered in urine as avibactam. The CL_R of avibactam in vivo (Study D4280C00008; in which [^{14}C]-labeled avibactam was administered) suggests that active secretion also contributes to the excretion of avibactam in addition to filtration by the kidney. The CL_R was 9.48 L/h (equivalent to 158 mL/min) on average, which is greater than the glomerular filtration rate. This is consistent with the observation that avibactam is a substrate of the renal transporters OAT1 and OAT3. The overall $T_{½}$ of avibactam following IV infusion is approximately 2 hours across studies.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Ceftazidime exhibits linear PK in the dose range of 500 to 2000 mg (Fortaz® US Prescribing Information).

In general, exposure to avibactam (C_{max} and AUC) increased approximately in proportion to increases in dose.

In Study NXL104-1001, exposure to avibactam (C_{max} and $AUC_{0-\infty}$) increased approximately in proportion to increases in dose following single-dose avibactam administration as a 30-minute IV infusion over a dose range of 50 to 2000 mg (Figure 14).

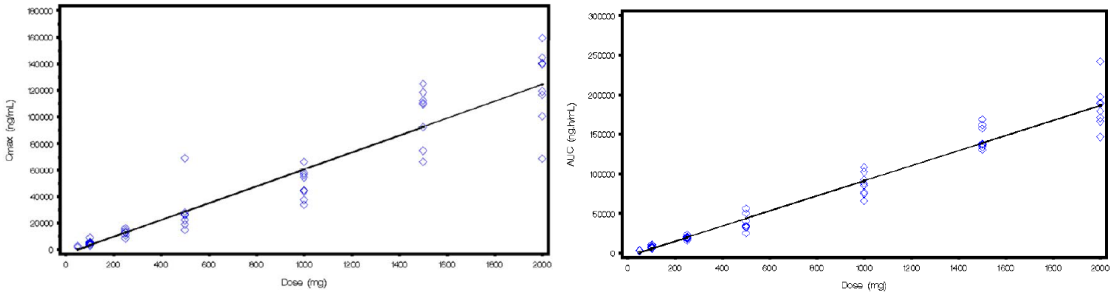


Figure 14. Relationship between C_{max} (Left panel) and $AUC_{0-\infty}$ (Right panel) *vs.* dose of avibactam following a single 30-min IV infusion to healthy adult male subjects (Study NXL104-1001)

In the repeated ascending dose study (Study NXL104-1002), avibactam was administered as 30-minute IV infusions q8h to healthy male subjects in the dose range 500 to 1000 mg. The results are shown in Table 19. For the 500-mg dose, there was large variability in C_{max} due to 1 subject, and $AUC_{0-\infty}$ was somewhat higher than expected. There was a dose-proportional increase of $AUC_{0-\infty}$ between the 750- and 1000-mg doses. Also, as shown in Table 19, the CL and $T_{½}$ were similar between doses, indicating linear PK of avibactam.

Table 19. PK parameters (geometric mean [CV%]) of avibactam following 30-min avibactam IV infusions q8h in healthy male subjects (Study NXL104-1002)

PK parameter	***500 mg q8h***		***750 mg q8h***		***1000 mg q8h***	
	Day 1 (N = 8)	*Day 5 (N = 8)*	*Day 1 (N = 8)*	*Day 5 (N = 8)*	*Day 1 (N = 8)*	*Day 5 (N = 8)*
C_{max} (µg/mL)	37.29 (70)	NA	40.78 (36)	NA	57.48 (20)	NA
$C_{max,ss}$ (µg/mL)	NA	36.33 (111)	NA	44.44 (26)	NA	50.90 (41)
T_{max}[a] (h)	0.5 (0.5-0.5)	0.5 (0.5-0.75)	0.5 (0.5-0.75)	0.5 (0.5-4.0)	0.5 (0.5-0.5)	0.5 (0.5-0.75)
$T_{½}$ (h)	1.44 (9)	1.66 (11)	1.37 (8)	1.34 (23)	1.37 (15)	1.47 (6)
$AUC_{0-\infty}$ (µg·h/mL)	53.12 (28)	NA	61.48 (18)	NA	82.76 (23)	NA
$AUC_{0-\tau}$ (µg·h/mL)	NA	50.63 (32)	NA	68.13 (23)	NA	82.08 (21)
CL (L/h)	9.41 (19)	9.88 (21)	12.20 (18)	11.01 (21)	12.08 (23)	12.18 (19)

[a] Median (minimum-maximum)

2.2.5.9. How do the PK parameters change with time following chronic dosing?

Because of the short $T_{½}$ of avibactam, no appreciable accumulation was observed after multiple dosing when avibactam was administered as a 60-minute IV infusion of 400 mg q8h, 600 mg q8h or q12 h, and 900 mg q12h. The PK after 400 mg q8h, 600 mg q8h, and 900 mg q12h dosing regimens are shown in Table 20 (Study CXL-PK-01). It should be noted that there is no substantial interaction between avibactam and ceftaroline fosamil. Following 10-day repeated IV dosing of avibactam (in combination with ceftaroline fosamil), ratios of Day 10 to Day 1 AUC_{0-24} ranged from 0.80 to 1.43, suggesting that there was no appreciable accumulation of avibactam either in a q12h or q8h dosing regimen. Dose-normalized C_{max} and AUC_{0-24} were similar across the treatment groups. The T_{max}, $T_{½}$, CL, and V_z were similar between a single dose (Day 1) and repeated dosing (Day 10) across the doses tested in this study and appeared to be dose independent. The $T_{½}$ was approximately 1.7 hours on Day 1 when avibactam was administered at

doses up to 900 mg. The CL for avibactam was approximately 11 L/h and was similar between the single doses and at steady state, indicating linear and time invariant PK.

Table 20. PK parameters (geometric mean [CV%]) of avibactam following 1-h avibactam IV infusions q8h or q12h in healthy male subjects (Study CXL-PK-01)

PK parameter	***400 mg q8h***		***600 mg q8h***		***900 mg q12h***	
	Dose (Day 1) (N = 9)	*Dose (Day 10) (N = 9)*	*Dose (Day 1) (N = 9)*	*Dose (Day 10) (N = 9)*	*Dose (Day 1) (N = 9)*	*Dose (Day 10) (N = 9)*
C_{max} (μg/mL)	18.43 (8.4)	18.69 (12.8)	29.69 (13.9)	31.24 (14.4)	48.15 (17.5)	49.31 (14.7)
T_{max} (h)[a]	0.98 (0.97-1.0)	0.98 (0.98-1.08)	1.0 (0.98-1.05)	0.98 (0.98-1.08)	0.98 (0.98-1.08)	0.98 (0.67-1.08)
$T_{½}$ (h)	1.70 (17.7)	1.72 (18.1)	1.67 (10.4)	1.78 (19.3)	1.73 (16.8)	1.78 (21.9)
$AUC_{0-\infty}$ (μg·h/mL)	33.98 (11.0)	NA	52.74 (10.8)	NA	82.89 (16.2)	NA
$AUC_{0-\tau}$ (μg·h/mL)	NA	33.96 (11.2)	NA	56.41 (11.8)	NA	86.98 (15.1)
CL (L/h)	11.77 (11.0)	11.44 (11.7)	11.38 (10.8)	10.32 (11.8)	10.86 (16.2)	10.28 (15.2)
CL_R (L/h)	8.92 (16.9)	9.87 (15.4)	9.08 (18.3)	8.26 (15.9)	9.02 (22.6)	8.86 (16.8)
Rac $AUC_{0-\tau}$	NA	1.03 (6.2)	NA	1.09 (15.9)	NA	1.05 (6.2)

2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The total variability for single dose ceftazidime and avibactam C_{max} and AUC_{inf} was low with CV% of <30% in healthy volunteers. The within-subject variability could not be estimated from the population PK analysis, because of lack of data on repeat dosing.

2.3. Intrinsic Factors

Age and Gender

The PK of ceftazidime is similar in adult males and females, and there are no gender-based dosing adjustments (FORTAZ package insert, 2010).

The effect of age and gender on the PK of avibactam was studied in healthy young (18 to 45 years of age) and elderly (≥ 65 years of age) male and female subjects (Study NXL104/1004). In this study, 500 mg avibactam was given as a single 30-minute IV infusion. An analysis of the overall effect of age and gender on avibactam plasma PK data was conducted for area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), area under the plasma concentration-time curve from time 0 to time t corresponding to the last quantifiable concentration (AUC_{0-t}), and C_{max} using an analysis of variance (ANOVA) model applied to log-transformed data with a class effect for the age and gender groups (Table 20). The analysis showed a significant age effect for AUC ($p < 0.05$); however, the increase in AUC was only 17% in the elderly compared to the young. There was no significant age effect for C_{max}. The analysis showed a significant gender effect for C_{max} ($p = 0.0288$); however, the decrease in C_{max} was only 18% in males compared to females. There was no significant gender effect for AUC. The

apparent $T_{½}$ was somewhat prolonged in elderly males and females (3.12 and 2.39 hours, respectively) compared to young males and females (2.02 and 1.71 hours, respectively). This may be attributed to the expected decrease in renal function in the elderly.

Although there were some age- and gender-related differences observed in the PK of avibactam, these differences were minor and do not impact dosing recommendations for CAZ-AVI. Age and gender were not identified as significant covariates in population PK analyses for avibactam or ceftazidime (Table 21).

Table 21. Summary of cohort comparisons of age and gender (Study NXL104/1004)

Parameter	Group	Effect	LS means[a]	Ration of LS means		90% CI	P-value
$AUC_{0-\infty}$ (µg·h/mL)	Age	Elderly	57.8	Elderly/young	1.17	(1.05, 1.31)	0.0218
		Young	49.3				
	Gender	Male	50.6	Male/Female	0.90	(0.80, 1.00)	0.1139
		Female	56.3				
AUC_{0-t} (µg·h/mL)	Age	Elderly	57.5	Elderly/young	1.17	(1.05, 1.31)	0.0253
		Young	49.1				
	Gender	Male	50.4	Male/Female	0.90	(0.80, 1.01)	0.1281
		Female	56.0				
C_{max} (µg/mL)	Age	Elderly	30.6	Elderly/young	0.88	(0.76, 1.02)	0.1621
		Young	34.7				
	Gender	Male	29.5	Male/Female	0.82	(0.70, 0.95)	0.0288
		Female	36.0				

[a] Units for LS means:
CI Confidence interval; LS Least-squares.

Race

There is no information on the influence of race in the ceftazidime product information (FORTAZ package insert, 2010).

One Phase 1 study was performed to characterize the PK of avibactam and ceftazidime in healthy Japanese male subjects (Study D4280C00010). In this study, a dose of 500 mg avibactam was given alone or in combination with 2000 mg ceftazidime as a 2-hour IV infusion and PK data were collected after a single dose and after q8h administration for 4 days. The study enrolled 16 Japanese male subjects. Six subjects received avibactam alone, and 7 subjects (n = 6 in PK evaluation) received CAZ-AVI. The PK of avibactam was similar when administered alone and in combination with ceftazidime, as well as between single and multiple doses. Thus, the effects of race on the PK of CAZ and AVI were evaluated with the PK data after the CAZ-AVI administration at steady state (PK collected on Day 7; q8h dosing). Since Study D4280C00010 did not include a non-Japanese control group, comparisons are made to the corresponding data from Study D4280C00011 (Part A), which had a similar design (PK collected on Day 11; q8h dosing), and in which 16 subjects (12 non-Japanese/4 Asian) were given multiple doses of CAZ-AVI.

In a cross-study comparison, the PK of avibactam was similar between Japanese and non-Japanese healthy subjects (Table 22). Some differences in ceftazidime PK were observed in the cross-study comparison (Table 23). The Japanese subjects in Study D4280C00010 had approximately 25% higher $C_{max,ss}$, 19% higher $AUC_{0-t,ss}$, 16% lower CL, and 22% lower V_{ss}

compared to the non-Japanese subjects. However, the observed differences in ceftazidime PK between these studies are modest, so dose adjustments based on race are not considered necessary.

Table 22. Avibactam PK parameters (geometric mean [CV%]) at steady state after the last dose of 500 mg avibactam + 2000 mg ceftazidime 2-hour IV infusion q8h in Japanese (Study D4280C00010) and non-Japanese subjects (Study D4280C00011 Part A; Day 11)

PK parameter	***Japanese subjects (N = 6)***	***Non-Japanese subjects (N = 16; 12 non-Japanese/4 Asian)***
$C_{max,ss}$, µg/mL	15.00 (20.6)	14.6 (17.0)
$T_{max,ss}$,[a] h	1.97 (1.00-1.97)	2.00 (2.00-2.02)
$T_{½}$,[b] h	1.37 (8.58)	2.71 (24.7)
$AUC_{0-t,ss}$, µg.h/mL	43.8 (15.1)	39.8 (19.1)
CL, L/h	11.9 (14.4)	13.1 (18.9)
CL_R,[c] L/h	9.41 (17.5)	12.8 (46.1)
V_{ss}, L	19.9 (13.1)	22.2 (17.8)
Ae, mg	475 (14.4)	543 (24.7)

[a] Median (minimum-maximum).
[b] The T½ was determined from plasma samples collected 0 to 8 hours post-dose in Japanese subjects and from plasma samples collected up to 24 hours post-dose in non-Japanese subjects.
[c] Calculated after the first (single) dose on Day 1 (not at steady state).
Ae: Amount excreted in urine unchanged (0-24 h after last dose at steady state);

Table 23. Ceftazidime PK parameters (geometric mean [CV%]) at steady state after the last dose of 500 mg avibactam + 2000 mg ceftazidime 2-h IV infusion q8h in Japanese (Study D4280C00010) and non-Japanese subjects (Study D4280C00011 Part A; Day 11)

PK parameter	***Japanese subjects (N = 6)***	***Non-Japanese subjects (N = 16; 12 non-Japanese/4 Asian)***
$C_{max,ss}$, µg/mL	113 (15.3)	90.4 (15.7)
$T_{ss,max}$,[a] h	1.97 (1.97-1.97)	2.00 (1.50-2.02)
$T_{½}$, h	1.68 (4.93)	2.76 (7.4)
$AUC_{0-t,ss}$, µg h/mL	377 (17.0)	316 (15.2)
CL, L/h	5.74 (17.2)	6.86 (15.2)
CL_R,[b] L/h	5.78 (14.0)	7.01 (20.1)
V_{ss}, L	13.3 (20.1)	17.0 (16.4)
Ae, mg	1930 (4.39)	2210 (8.1)

[a] Median (minimum-maximum).
[b] Calculated after the first (single) dose on Day 1 (not at steady state).
Ae: Amount excreted in urine unchanged (0-24 h after last dose at steady state);

Obesity

There is no information on the effect of obesity on the PK of ceftazidime in the product label (FORTAZ package insert, 2010).

The impact of obesity on the PK of avibactam was explored in healthy young subjects in the CXL development program, where single doses of 600 mg ceftaroline fosamil/600 mg avibactam were administered as a 60-minute IV infusion (Study CXL-PK-06). Since ceftaroline fosamil did not affect the systemic exposure of avibactam in Study CXL-PK-01 (see section 2.4), it is acceptable the use of avibactam PK data from the CXL program to evaluate the impact of obesity on the PK of avibactam. Because avibactam PK is linear (see section **2.2.5.8**), it is also acceptable to apply the results of this study with 600 mg avibactam administered as 60 minutes infusion to the avibactam dose is 500 mg in the CAZ-AVI formulation.

Study CXL-PK-06 had 4 cohorts (24 males and 16 females; 18 to 45 years of age; n =10/cohort): 1) normal to overweight subjects (BMI 18.5 to 29.9 kg/m^2; body weight 50 to 100 kg), 2) obese class I (BMI 30 to 34.9 kg/m^2; body weight 90 to 115 kg), 3) obese class II (BMI 35 to 39.9 kg/m^2; body weight 105 to 130 kg), and 4) obese class III (BMI $\geq$ 40 kg/m^2; body weight $\geq$ 120 kg). Subjects in Cohorts 1 and 2 were age, gender, race, and renal function matched to the subjects in Cohorts 3 and 4, on an individual basis. The avibactam plasma concentration versus time profiles are shown in Figure 15 for the different cohorts and the PK parameters for avibactam are summarized in Table 24.

For subjects in the obese classes I, II, and III cohorts, the geometric mean C_{max} of avibactam following a single dose of 600 mg/600 mg CXL was 13.5%, 19.7%, and 38.4%, lower, respectively, than the C_{max} value in subjects who were normal to overweight. The geometric mean $AUC_{0-\infty}$ of avibactam was lower by 10.5%, 18.4%, and 20.0%, respectively, and apparent volume of distribution was higher in subjects who were obese than in subjects who were normal to overweight. The $T_{½}$ and T_{max} of avibactam were similar across all weight groups. In all subjects, nearly the entire administered dose of avibactam was excreted in the urine within 24 hours. Statistically significant differences were also noted for V_{ss} between obese class II and III subjects compared to normal to overweight subjects, with the biggest difference between obese class III (V_{ss} = 37.75 L) versus normal to overweight subjects (V_{ss} = 21.12 L).

The efficacy of avibactam is associated with time above a C_T over the dosing interval (see section **2.2.4.1**), and as depicted in Figure 15, there is a minor effect on the terminal part of the concentration versus time curves for the different groups in this study. Therefore, based on the results from this study, dosing adjustments of avibactam due to obesity are not warranted in obese class I, II, and III subjects.

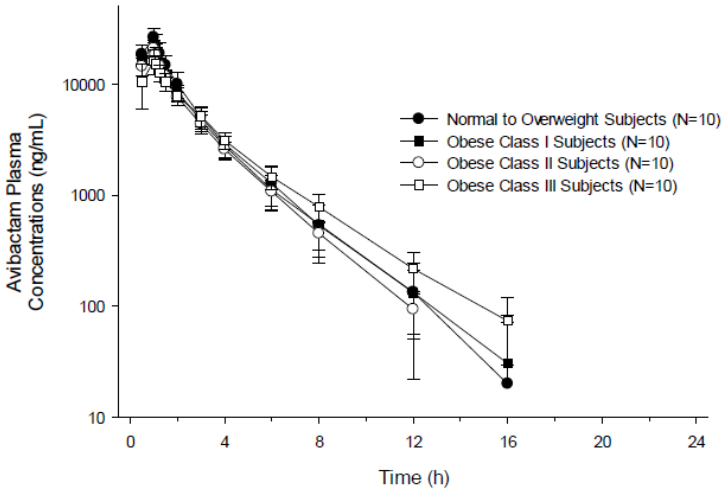


Figure 15. Mean (± SD) avibactam plasma concentration (ng/mL) vs time curves after a 600-mg avibactam dose given as a 60-min IV infusion (Study CXL-PK-06)

Table 24. PK parameters (geometric mean [CV%]) of avibactam in subjects with normal BMI/body weight and with different degrees of obesity after a single 600-mg avibactam 60-min IV infusion (Study CXL-PK-06)

PK parameter	***Healthy or overweight (BMI 18.5-29.9) (N = 10)***	***Obese class I (BMI 30-34.9) (N = 10)***	***Obese class II (BMI 35-39.9) (N = 10)***	***Obese class III (BMI 35- ≥ 40) (N = 10)***
C_{max}, µg/mL	25.68 (21.6)	22.21 (8.7)	20.62 (13.4)	15.81 (24.2)
T_{max},[a] h	1.00 (0.97-1.08)	1.03 (0.98-1.08)	1.01 (0.93-1.08)	1.00 (0.95-1.13)
$T_{½}$, h	1.82 (22.9)	1.91 (23.0)	1.71 (9.0)	2.21 (15.4)
AUC_{0-t}, µg.h/mL	48.59 (21.1)	43.45 (10.5)	39.57 (12.0)	38.79 (17.9)
$AUC_{0-\infty}$, µg.h/mL	48.90 (21.2)	43.75 (10.4)	39.88 (11.9)	39.09 (17.7)
CL, L/h	12.27 (21.2)	13.72 (10.4)	15.05 (11.9)	15.35 (17.7)
CL_R, L/h	10.6 (45.7)	13.93 (13.5)	14.20 (30.4)	14.25 (31.7)
V_z,[b] L	32.22 (29.5)	37.82 (21.4)	37.14 (17.2)	49.02 (19.1)
V_{ss},[b] L	21.12 (25.5)	24.83 (12.8)	26.66 (15.5)	37.75 (26.9)
Ae_{0-t}, mg	515.2 (49.3)	605.2 (6.0)	562.0 (30.7)	552.9 (21.8)
Ae_{0-t}, % dose	85.87 (49.4)	100.86 (6.0)	93.66 (30.7)	92.15 (21.8)

[a] Median (minimum-maximum).
Ae_{0-t}: Amount excreted in urine from time 0 to time t;

Renal Impairment

The major route of elimination of ceftazidime is by the kidney. Various dose reductions and/or changes in dosing frequency are recommended starting in patients with moderate renal impairment with a CrCL ≤ 50 mL/min (FORTAZ® US Prescribing Information). It should be noted that the proposed dosing regimen of CAZ-AVI for patients with renal impairment (see section **2.1.3**) is identical as the recommended dosing regimen of FORTAZ for patients with renal impairment.

Avibactam is also mainly eliminated via the kidney. Therefore, the PK of avibactam has been studied in subjects with varying degrees of renal impairment after single doses of avibactam alone (Study NXL104/1003; 100 mg as a 30-minute IV infusion) and after repeated doses in combination with ceftaroline fosamil as part of the CXL development program in subjects with severe renal impairment (300 mg ceftaroline fosamil/125 mg avibactam) with matched controls with normal renal function (600 mg ceftaroline fosamil/600 mg avibactam) (Study CXL-PK-03; 60-minute IV infusion q8h). The Cockroft-Gault formula was used to estimate CrCL in both studies.

As expected, in Study NXL 104/0003, the CL of avibactam after a single 100-mg dose decreased significantly in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function (Table 25). The CL was 15 L/h in subjects with normal renal function and decreased to 5.8 L/h in subjects with mild renal impairment (2.6-fold decrease). The decrease was more pronounced in subjects with moderate renal impairment and non-dialyzed subjects with severe renal impairment with mean CL of 3.8 L/h (3.8-fold decrease) and 2.2 L/h (7.1-fold decrease), respectively. It reached a residual value of about 1.0 L/h (15-fold decrease) in subjects with end-stage renal disease (ESRD) (off dialysis). Accordingly, the exposure of avibactam was increased with the decrease in CL of avibactam in mild, moderate, and severe renal impairment compared to subjects with normal renal function (Table 25 and Figure 16).

Table 25. Avibactam PK parameters (geometric mean [CV%]) following a single 30-min IV Infusion of 100 mg avibactam in subjects with varying degrees of renal impairment (Study NXL104/1003)

PK parameter	***Renal function***				
	Normal (CrCL > 80 mL/min) N = 6	*Mild impairment (CrCL 50-79 mL/min) N = 6*	*Moderate impairment (CrCL 30-49 mL/min) N = 6*	*Severe impairment (CrCL < 30 mL/min) N = 6*	*ESRD Off dialysis N = 6*
C_{max}, µg/mL	4.65 (7.66)	5.61 (24.99)	5.67 (44.76)	6.65 (27.37)	6.53 (27.62)
Ratio C_{max}[a] (p-value)	—	1.207 (NS)	1.219 (NS)	1.428 (NS)	1.402 (NS)
$T_{½}$, h	1.76 (18.06)	4.00 (103.3)	5.23 (32.55)	7.66 (19.97)	22.82 (52.45)
$AUC_{0-\infty}$, µg h/mL	6.68 (7.97)	17.55 (31.69)	25.64 (17.78)	47.08 (51.65)	130.62 (55.43)
Ratio AUC[a] (p-value)	—	2.626 (0.0005)	3.836 (< 0.0001)	7.044 (< 0.0001)	19.544 (< 0.0001)
CL, L/h	14.96 (7.74)	5.70 (27.59)	3.90 (15.05)	2.12 (39.38)	0.77 (82.44)
Ratio CL[a] (p-value)	—	0.381 (0.0005)	0.261 (< 0.0001)	0.142 (< 0.0001)	0.051 (< 0.0001)
CL_R, L/h	11.93[b](14.35)	4.56[b] (49.10)	2.96[b] (25.57)	1.28[b] (43.69)	—
fe (%dose)	79.96[b] (15.99)	81.23[b] (41.43)	75.85[b] (24.22)	54.89[b] (8.40)	—

[a]: Ratio of geometric means (reference = normal renal function).
[b]: Arithmetic mean.
ESRD End-stage renal disease; fe Percent dose excreted unchanged in urine; NS Not statistically significant (p > 0.2)

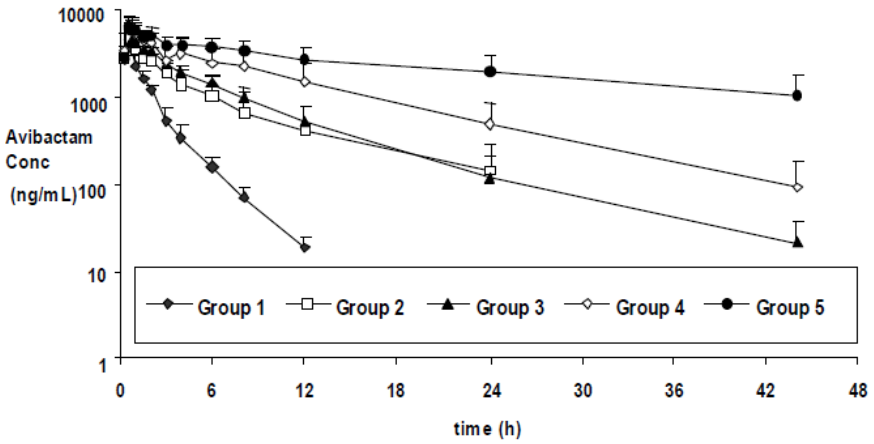


Figure 16. Mean (± SD) plasma concentration of avibactam vs time profiles (log/linear scale) after a 30-min IV infusion of 100 mg in subjects with normal renal function (Group 1), mild (Group 2), moderate (Group 3), and severe (Group 4) renal impairment, and ESRD off dialysis (Group 5) (Study NXL104/1003)

In Study NXL104/1003, the effect of dialysis was also investigated in the subjects with ESRD. The extraction coefficient during dialysis was calculated to be 0.77, with low inter-individual variability (8.8% CV). The mean hemodialysis clearance was 8.97 L/h, corresponding to approximately 75% of the CL_R observed in healthy subjects with normal renal function (mean CL_R = 11.93 L/h). During the 4-hour dialysis session, 55% of the avibactam dose was removed. In Study CXL-PK-03, the mean $AUC_{0-\infty}$ was 25.6% higher in subjects with severe renal impairment administered 125 mg avibactam q8h in combination with ceftaroline fosamil than in subjects with normal renal function administered 600 mg avibactam q8h. These results are consistent with the decrease in CL for avibactam observed in subjects with severe renal impairment in Study NXL104/1003. The V_{ss} of avibactam was similar in Study CXL-PK-03 for subjects with severe renal impairment and normal renal function (approximately 20 L), as expected for a drug with low plasma protein binding.

The PK after single doses of ceftaroline fosamil in combination with avibactam (600 mg ceftaroline fosamil/600 mg avibactam, 60-minute IV infusions) was studied in 12 patients with augmented renal clearance (ARC, measured CrCL > 140 mL/min) and sepsis (Study CXL-PK-04). In these patients, CrCL was calculated from measured urinary creatinine collected over an 8-hour interval. Nine of the 12 patients were on ventilator support, and the mean measured CrCL (± standard deviation [SD]) was 194.85 ± 76.09 mL/min. The PK parameters of avibactam are presented in Table 26. The mean CL of avibactam was 39.5% greater, resulting in a 28.4% lower AUC_{0-t} and a 37.8% reduction in C_{max}, in patients with ARC and sepsis compared to healthy subjects with normal renal function (cross-study comparison to Study CXL-PK-01).

Table 26. Avibactam PK parameters (geometric mean [CV%]) after a single 60-min IV infusion of 600 mg/600 mg ceftaroline fosamil/avibactam in patients with augmented renal clearance and sepsis (Study CXL-PK-04)

PK parameter	***Avibactam (N = 10)***
C_{max}, μg/mL	18.09 (9.7)
$T_{½}$, h	1.63 (23.4)
AUC_{0-t}, μg.h/mL	36.75 (19.1)
$AUC_{0-\infty}$, μg.h/mL	37.05 (19.3)
V_{ss}, L/h	26.51 (17.2)
CL, L/h	16.30 (18.8)

Dose Adjustment for patients with renal impairment: The predicted exposure (i.e., C_{max} and AUC) of ceftazidime and avibactam by renal category for the simulation of patients with cIAI receiving the sponsor's originally proposed dosing is provided in Table 27. The largest increase in exposure relative to subjects with normal renal function was in the mild renal impairment group. The mean $AUC_{0-24,ss}$ was 39% higher for avibactam and 52% higher for ceftazidime in simulated patients with cIAI and mild renal impairment compared to $AUC_{0-24,ss}$ in simulated subjects with normal renal function. However, the predicted $AUC_{0-24,ss}$ values in patients with cIAI and mild renal impairment (131 μg·h/mL and 828 μg·h/mL for avibactam and ceftazidime, respectively) are similar to the observed values following 11 days of dosing with 2.5 g CAZ-AVI in healthy subjects with normal renal function in Study D4280C00011 (114.6 μg·h/mL and 873 μg·h/mL for avibactam and ceftazidime, respectively), indicating that there would be no safety issue of the proposed dosing for patients with mild renal impairment.

Table 27. Summary of PK parameter values (Mean±SD) in simulated cIAI subject population for different renal function groups (5000 simulated subjects per group) with CAZ-AVI given as a 2-hour IV infusion

Renal Function	Proposed Dose Regimen	Ceftazidime		Avibactam	
		$C_{max,ss}$ (μg/mL)	$AUC_{0-24,ss}$ (μg·h/mL)	$C_{max,ss}$ (μg/mL)	$AUC_{0-24,ss}$ (μg·h/mL)
NORM	2000 mg CAZ + 500 mg AVI, q8h	47.2±13.4	542±161	9.31±1.87	93.5±21.3
MILD	2000 mg CAZ + 500 mg AVI, q8h	59.9±17.1	828±260	11.2±2.37	131±36.4
MODE	1000 mg CAZ + 250 mg AVI, q12h	33.5±9.6	448±142	6.84±1.48	80.3±22.8
SEV1	1000 mg CAZ + 250 mg AVI, q24h	33.9±10.2	400±136	7.61±1.85	82.8±26.7
SEV2	500 mg CAZ + 125 mg AVI, q24h	27.0±9.03	455±180	6.79±2.07	116±47.6
ESRD	500 mg CAZ + 125 mg AVI, q48h	45.7±22.9	898±527	5.26±1.04	75.6±16.8

NORM Normal renal function (CrCL > 80 mL/min); MILD Mild renal impairment (51 mL/min ≤ CrCL ≤ 80 mL/min); MODE Moderate real impairment (31 mL/min ≤ CrCL ≤ 50 mL/min); SEV1 Severe renal impairment (16 mL/min ≤ CrCL ≤ 30mL/min); SEV2 Severe renal impairment (6 mL/min ≤ CrCL ≤ 15 mL/min); ESRD End-stage renal disease (0 mL/min < CrCL ≤ 5 mL/min).

It should be noted that the predicted exposure (i.e., C_{max} and AUC) of ceftazidime and avibactam in the simulated patients with moderate (31 mL/min ≤ CrCL ≤ 50 mL/min) and severe [SEV1 (16 mL/min ≤ CrCL ≤ 30mL/min) and SEV2 (6 mL/min ≤ CrCL ≤ 15 mL/min)] renal

impairment receiving the originally proposed dosing regimens were substantially lower compared with the simulated patients with normal renal function (Table 27) although the proposed dosing for patients with different renal function provides ~100% probability of joint PK/PD target attainment (i.e., 50%*f*T > MIC for ceftazidime and 50%*f*T > 1.0 mg/L) at up to 8 µg/mL of MIC (see Table 15 in Section **2.2.4.1**). Figure 17 shows that predicted concentration-time profiles of ceftazidime and avibactam in the simulated patients with normal renal function *vs.* moderate renal impairment receiving the originally proposed dosing regimen.

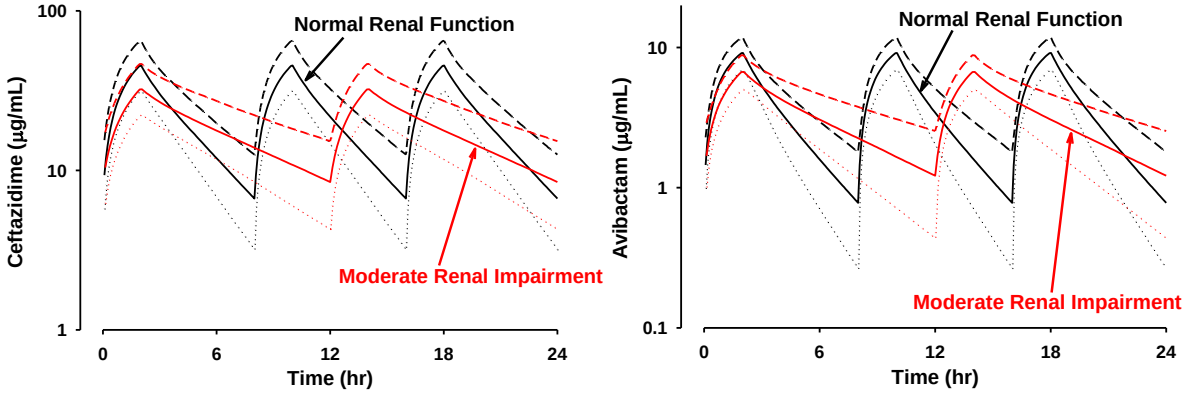


Figure 17. Concentration-time profiles of ceftazidime (right panel) and avibactam (left panel) in simulated patients with normal renal function (Black lines: 2000 mg CAZ + 500 mg AVI, q8h) and moderate renal impairment (Red lines: 1000 mg CAZ + 250 mg AVI, q12h). N=5000 per each group. Solid lines represent the median values. Broken and dotted lines represent 90th and 10th percentiles, respectively.

On October 9 and 16, 2014, the sponsor submitted two amendments (efficacy results only of an ongoing cIAI Phase 3 study) to provide new clinical information regarding a lower cure rate in patients with moderate renal impairment. A subgroup analysis indicated that for cIAI patients with moderate renal impairment (i.e., estimated creatinine clearance [CrCL] ≤ 50 mL/min) at study baseline ("MRIB" subgroup) those treated with CAZ-AVI had a lower clinical cure rate compared with patients treated with meropenem (Table 28). In patients with normal renal function or mild renal impairment at baseline, the clinical cure rates were similar across treatment arms and higher in each case than the cure rate for the corresponding MRIB subgroup (Table 28). With the up-to-date information submitted by the sponsor, it is not clear why the MRIB subgroup treated with CAZ-AVI had a lower clinical cure rate.

Table 28. Summary of clinical cure rate at test of cure, by baseline renal function subgroup [Phase 3 cIAI Study (Studies 4280C00001 and 4280C00005); mMITT Analysis Set)]

Baseline Renal Function Subgroup	***CAZ-AVI + MTZ n/N1 (%)***	***Meropenem n/N1 (%)***
Normal function/mild impairment (CrCL > 50 mL/min)	322/379 (85)	321/373 (86)
Moderate impairment (CrCL > 30 to ≤ 50 mL/min)	14/31 (45)	26/35 (74)

mMITT = microbiologically Modified Intent-to-Treat; MTZ = metronidazole; n = number of patients with clinical cure; N1 = total number of patients.

Collectively, the dosing regimens of CAZ-AVI for patients with <50 mL/min of CrCL warrant revision because of (a) a lower clinical cure rate in patients with moderate renal impairment receiving the proposed CAZ-AVI dosing regimen, (b) the ceftazidime and avibactam exposure is substantially lower in patients with moderate or severe renal impairment compared to patients with normal renal function, and (c) the FORTAZ label allows for a 50% increase in ceftazidime dose for renally impaired patients with severe infections. It should be noted that the proposed dose adjustments in the original NDA are predicted to result in adequate PK/PD target attainment for pathogens with CAZ-AVI MICs up to 8 mg/L (See Table 15 in Section **2.2.4.1**).

As recommended in the FORTAZ label, 50% higher daily doses were evaluated for patients with moderate or greater renal impairment. Considering the uncertainty of the PK/PD targets determined in animal models, the above reasons (a) and (b) were important to consider in determining the CAZ-AVI dosing regimens for patients with renal impairment. Accordingly, it is recommended to revise the CAZ-AVI dosing regimens for patients with renal impairment as shown in Table 29. Table 29 also summarizes the PK parameters predicted from simulated patients receiving the revised CAZ-AVI dosing regimens. Figure 18 shows the concentration-time profiles of ceftazidime and avibactam in patients with differing renal function receiving the revised CAZ-AVI dosing regimens. The revised CAZ-AVI dosing regimens are predicted to provide patients with <50 mL/min of CrCL with comparable exposure of ceftazidime and avibactam to patients with normal renal function receiving 2000 mg CAZ + 500 mg AVI Q8h, but still lower than patients with mild renal impairment receiving 2000 mg CAZ + 500 mg AVI Q8h. Since the exposure of both ceftazidime and avibactam is highly dependent on renal function, for patients presumed to have rapidly improved renal function during the period of drug treatment, it is recommended to monitor CrCL frequently and adjust the CAZ-AVI dose accordingly.

Table 29. Summary of PK parameter values [Median (Geometric CV as %)] in simulated cIAI subject population for different renal function groups (5000 simulated subjects per group) with CAZ-AVI given as a 2-hour IV infusion

Renal Function	Newly Proposed Dose Regimen	Ceftazidime		Avibactam	
		$C_{max,ss}$ (μg/mL)	$AUC_{0-24,ss}$ (μg·h/mL)	$C_{max,ss}$ (μg/mL)	$AUC_{0-24,ss}$ (μg·h/mL)
NORM	2000 mg CAZ + 500 mg AVI, q8h	45.5 (63)	518 (63)	9.17 (62)	91.2 (62)
MILD	2000 mg CAZ + 500 mg AVI, q8h	57.6 (63)	783 (64)	11.0 (62)	126 (63)
MODE	1250 mg CAZ + 250 mg AVI, q8h	39.5 (63)	643 (64)	7.87 (62)	116 (63)
SEV1	750 mg CAZ + 188 mg AVI, q12h	34.6 (63)	571 (64)	7.61 (62)	118 (64)
SEV2	750 mg CAZ + 188 mg AVI, q24h	38.6 (64)	628 (65)	9.70 (63)	158 (66)
ESRD	750 mg CAZ + 188 mg AVI, q48h	59.6 (67)	1120 (69)	7.78 (62)	111 (62)

NORM Normal renal function (CrCL > 80 mL/min); MILD Mild renal impairment (51 mL/min ≤ CrCL ≤ 80 mL/min); MODE Moderate real impairment (31 mL/min ≤ CrCL ≤ 50 mL/min); SEV1 Severe renal impairment (16 mL/min ≤ CrCL ≤ 30mL/min); SEV2 Severe renal impairment (6 mL/min ≤ CrCL ≤ 15 mL/min); ESRD End-stage renal disease (0 mL/min < CrCL ≤ 5 mL/min).

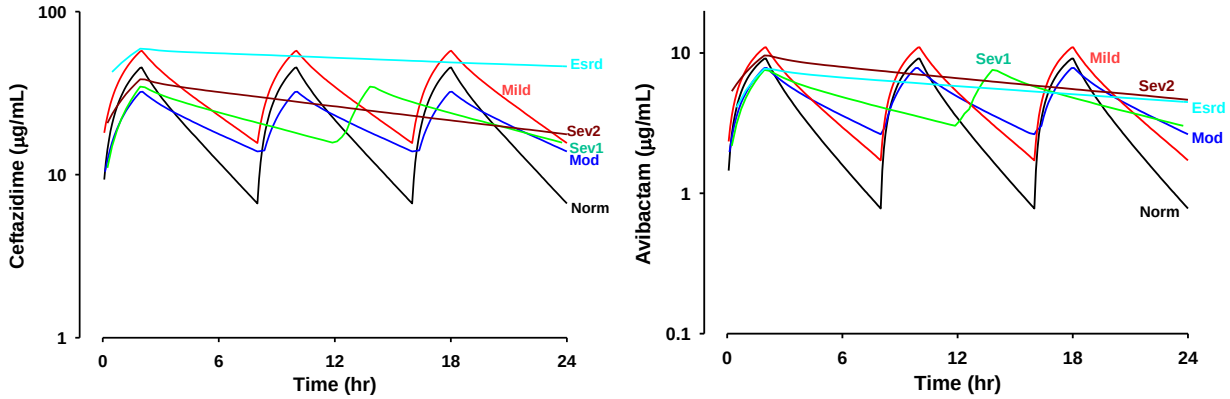


Figure 18. Steady-state concentration-time profiles of ceftazidime (right panel) and avibactam (left panel) in simulated patients with different levels of renal function receiving the revised dosing regimen: Normal (CrCL >80 mL/min, black line): 2000 mg CAZ + 500 mg AVI, q8h; Mild (CrCL 51-80 mL/min, red line): 2000 mg CAZ + 500 mg AVI, q8h); Moderate (CrCL 31-50 mL/min, blue line): 1250 mg CAZ + 250 mg AVI, q8h); SEV1 (CrCL 16-30 mL/min, green line): 750 mg CAZ + 188 mg AVI, q12h); SEV2 (CrCL 6-15 mL/min, dark red line): 750 mg CAZ + 188 mg AVI, q24h); ESRD (CrCL 0-5 mL/min, sky blue line): 750 mg CAZ + 188 mg AVI, q48h). N=5000 per each group. Lines represent the median values.

Alternative intervals of dosing (q8h and q12h) for patients with moderate reanl impairment were also evaluated. . The overall CAZ and AVI exposure and the probability of target attainment in patients with CrCL ≤50 mL/min are comparable for the two regimens [e.g., 1500 mg CAZ + 750 mg AVI, q12h (instead of 1250 mg CAZ + 250 mg AVI, q8h) for patients with CrCL 31- 50 ml/min]. However, the proposed dose in Table 29 offers better coverage if renal function rapidly improves before the dose can be re-adjusted. For example, if a patient with moderate renal impairment (CrCL of 31-50 mL/min) was receiving 1250 mg (1000 mg CAZ + 250 mg AVI) CAZ-AVI q8h and renal function improved to be in the range of normal renal function (CrCL > 80 mL/min) without dose adjustment, the probability of PK/PD target attainment would still be over 80% at an MIC of 4 mg/L. On the other hand, if a subject with moderate renal impairment was receiving 1875 mg (1500 mg ceftazidime + 375 mg avibactam) CAZ-AVI q12h and renal function improved to be in the range of normal without dose adjustment, target attainment at an MIC of 4 mg/L would only be 49.4%. Although less frequent dosing is preferred from a clinical practice perspective, the proposed dosing regimen in Table 29 was considered to be more appropriate because of an advantage in terms of the probability of target attainments for patient whose renal function rapidly improves before the dose is re-adjusted.

Hepatic Impairment

The presence of mild or moderate hepatic dysfunction had no effect on the PK of ceftazidime in individuals administered 2 g IV q8h for 5 days, provided renal function was not impaired (FORTAZ® US Prescribing Information).

The PK of avibactam in patients with hepatic impairment has not been established. Avibactam does not appear to undergo significant hepatic metabolism; therefore, the systemic clearance of avibactam is not expected to be significantly affected by hepatic impairment.

Because both ceftazidime and avibactam do not undergo hepatic metabolism *in vitro*, and the major route of elimination for both compounds is via the kidney, hepatic impairment is not expected to impact the PK of ceftazidime or avibactam after CAZ-AVI administration. Dose adjustments are not considered necessary for CAZ-AVI in patients with impaired hepatic function.

2.4. Extrinsic factors

Based on the results of *in vitro* studies (see section **2.2.5.6**), the potential for DDIs with CAZ-AVI is low. The only potential interaction identified was between avibactam and potent inhibitors of the renal transporters OAT1 and OAT3 (e.g., probenecid).

Three Phase 1 studies (Studies D4280C00011, D4280C00012, and CXL-PK-01) were conducted to determine if there were PK DDIs between avibactam and other drugs that will be administered with it in combination (ceftazidime, ceftaroline fosamil, and metronidazole). Two of these studies also evaluated PK DDIs for ceftazidime.

Study D4280C00011 (Part B) demonstrated that there was no DDI between avibactam and ceftazidime following either single-dose administration as a 2-hour IV infusion or when administered q8h as 2-hour IV infusions over 4 days to healthy male subjects. The 90% confidence intervals (CIs) for the geometric least-squares mean ratios of CAZ-AVI/avibactam alone and CAZ-AVI/ceftazidime alone were entirely contained within the range of 80% to 125% for $AUC_{0-\infty}$ and C_{max} on Day 1 and for AUC during the dosing interval ($AUC_{0-\tau}$) and $C_{max,ss}$ on Day 4 (Table 30).

Table 30. Statistical comparison of key pharmacokinetic parameters of avibactam and ceftazidime following 2-hour infusion of (a) 500 mg avibactam, (b) 2000 mg ceftazidime, and (c) 500 mg avibactam and 2000 mg ceftazidime. (Study D4280C00011)

						Pairwise Comparison		
Analyte	**Day**	**Parameter (unit)**	**Trt**	**n**	**Geo LS Mean**	**Pair**	**Ratio (%)**	**90% CI**
Avibactam	1	AUC (µg·h/mL)	A	25[a]	38.88			
			C	27	39.77	C/A	102.27	(100.63, 103.93)
		C_{max} (µg/mL)	A	27	13.94			
			C	27	14.21	C/A	101.97	(99.51, 104.50)
	4	$AUC_{(0-\tau)}$ (µg·h/mL)	A	27	38.51			
			C	27	37.81	C/A	98.18	(96.19, 100.22)
		C_{max} (µg/mL)	A	27	14.01			
			C	27	13.90	C/A	99.27	(96.70, 101.92)
Ceftazidime	1	AUC (µg·h/mL)	B	27	308.1			
			C	27	306.6	C/B	99.53	(96.47, 102.69)
		C_{max} (µg/mL)	B	27	94.40			
			C	27	93.60	C/B	99.16	(94.45, 104.09)
	4	$AUC_{(0-\tau)}$ (µg·h/mL)	B	27	306.8			
			C	26[b]	311.8	C/B	101.64	(98.77, 104.59)
		C_{max} (µg/mL)	B	27	99.43			
			C	26[b]	99.02	C/B	99.59	(94.58, 104.86)

Trt treatment; Geo geometric; LS least-squares; CI confidence interval.
Part B/Treatment A: 2-hour infusion of 500 mg avibactam;
Part B/Treatment B: 2-hour infusion of 2000 mg ceftazidime;
Part B/Treatment C: 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime.
[a] AUC values for 2 volunteers in Treatment A were not reported as Rsq (coefficient of determination for calculation of λz) was less than 0.8 for λz estimation.
[b] Pharmacokinetic parameters for Volunteer E0002025 in Treatment C of Part B were excluded due to an abnormal pharmacokinetic profile of ceftazidime on Day 4.

In Study D4280C00012, administration of CAZ-AVI (2000 mg ceftazidime + 500 mg avibactam) to healthy male subjects as a 2-hour infusion, following a 1-hour infusion of 500 mg metronidazole q8h for 3 days, did not affect the C_{max} and AUC values for avibactam or ceftazidime compared to administration of CAZ-AVI alone. The geometric least-squares mean ratios (CAZ-AVI + metronidazole/CAZ-AVI alone) for avibactam and ceftazidime $AUC_{0-\infty}$ and C_{max} on Day 1 and $AUC_{0-\tau}$ and $C_{max,ss}$ on Day 4 ranged from 96.3% to 104.8%, and the 90% CIs for the geometric least-squares mean ratios were all entirely contained within the interval of 80% to 125% (Table 31). Similarly, administration of 500 mg metronidazole to healthy male subjects as a 1-hour infusion before a 2-hour infusion of CAZ-AVI q8h for 3 days did not affect the $C_{max,ss}$ and $AUC_{0-\tau}$ of metronidazole compared to administration of 500 mg metronidazole alone (Table 31).

Table 31. Statistical comparison of key pharmacokinetic parameters of avibactam, ceftazidime, and metronidazole following IV administration of (a) ceftazidime 2000 mg + avibactam 500 mg (intravenous) over 2 hours, (b) metronidazole 500 mg (intravenous) over 1 hour, and (c) metronidazole 500 mg (intravenous) over 1 hour followed by ceftazidime 2000 mg + avibactam 500 mg (intravenous) over 2 hours. (Study D4280C00012)

						Pairwise Comparison		
Analyte	**Day**	**Parameter (unit)**	**Trt**	**n**	**Geo LS Mean**	**Pair**	**Ratio (%)**	**90% CI**
Avibactam	1	AUC (µg·h/mL)	A	28	37.81			
			C	28	39.57	C-A	104.66	(102.90, 106.45)
		C_{max} (µg/mL)	A	28	12.82			
			C	28	13.43	C-A	104.75	(102.54, 107.01)
	4	$AUC_{(0-\tau)}$ (µg·h/mL)	A	28	36.59			
			C	28	37.85	C-A	103.45	(101.38, 105.56)
		C_{max} (µg/mL)	A	28	13.04			
			C	28	13.25	C-A	101.60	(99.28, 103.98)
Ceftazidime	1	AUC (µg·h/mL)	A	28	254.0			
			C	28	254.1	C-A	100.04	(98.48, 101.62)
		C_{max} (µg/mL)	A	28	74.36			
			C	28	75.12	C-A	101.03	(98.93, 103.18)
	4	$AUC_{(0-\tau)}$ (µg·h/mL)	A	28	260.1			
			C	28	250.6	C-A	96.34	(94.98, 97.72)
		C_{max} (µg/mL)	A	28	78.68			
			C	28	77.56	C-A	98.59	(96.76, 100.45)
Metronidazole	1	AUC (µg·h/mL)[a]	B	21	108.4			
			C	23	105.5	C-B	97.28	(94.72, 99.91)
		C_{max} (µg/mL)	B	27	11.58			
			C	28	11.03	C-B	95.24	(91.55, 99.07)
	4	$AUC_{(0-\tau)}$ (µg·h/mL)	B	27	116.3			
			C	27[b]	122.7	C-B	105.50	(102.91, 108.15)
		C_{max} (µg/mL)	B	27	21.20			
			C	27[b]	21.69	C-B	102.30	(99.20, 105.49)

Trt: treatment; Geo: geometric; LS: least-squares; CI: confidence interval
Treatment A: Ceftazidime 2000 mg + avibactam 500 mg (intravenous) over 2 hours.
Treatment B: Metronidazole 500 mg (intravenous) over 1 hour.
Treatment C: Metronidazole 500 mg (intravenous) over 1 hour followed by ceftazidime 2000 mg + avibactam 500 mg (intravenous) over 2 hours.
[a] AUC for 6 volunteers in Treatment B and 5 volunteers in Treatment C were not reported due to $\%AUC_{ex}$ greater than 20%.
[b] Pharmacokinetic parameters for Volunteer E0001085 were excluded on Day 4 in Treatment C due to a protocol deviation.

In Study CXL-PK-01 (Part A), the geometric least-squares mean ratios (CXL/avibactam alone) for $AUC_{0-\infty}$ and C_{max} were 98.8% and 98.6%, respectively, and the 90% CIs for the geometric least-squares mean ratios were entirely contained within the interval of 80% to 125% (data are not presented). These results demonstrate that ceftaroline fosamil does not affect the systemic exposure of avibactam when these drugs are coadministered. Similarly, the systemic exposure of ceftaroline was not affected by coadministration of avibactam.

The clinical DDI studies and ceftazidime data from the ceftazidime label support the use of metronidazole in combination with CAZ-AVI for the treatment of cIAI, and the use of avibactam PK data from the CXL program.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Ceftazidime and avibactam were the active moieties measured in human plasma, urine, and bronchoalveolar lavage fluid using a high-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS-MS) detection in clinical pharmacology studies and clinical studies. The method validations and the bioanalyses for the respective clinical studies were conducted by (b) (4)

2.6.2. Which metabolites have been selected for analysis and why?

Metabolism is a minor route of elimination of CAZ-AVI, and there is no evidence that any ceftazidime and avibactam metabolites are pharmacologically/microbiologically active, and therefore no metabolites were analyzed.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Because less than 10% of both ceftazidime and avibactam were protein bound and plasma protein binding of both compounds are not concentration-dependent, total drug concentrations (bound plus free) of ceftazidime and avibactam were measured in human plasma, urine, and bronchoalveolar lavage fluid.

2.6.4. What bioanalytical methods are used to assess concentrations?

High-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS-MS) detection was used to support clinical studies. All methods entailed use of stable isotope-labeled internal standards in support of ceftazidime and avibactam quantification except for method HFL100567/1, in which stable isotope-labeled avibactam only was used for the quantification of both avibactam and ceftazidime, and method HFL100568/1, in which an analogue internal standard (b) (4) was used for quantification of ceftazidime.

Human plasma study samples were collected and stabilized using sodium fluoride/potassium oxalate tubes for all studies except study CXL-PK-01, in which the sodium fluoride/potassium oxalate plasma study samples were further treated with a protease inhibitor cocktail. Plasma sample preparation prior to HPLC/MS-MS was carried out either by protein precipitation or solid phase extraction.

Human urine samples were stabilized with acetic acid, except for studies CXL-PK-01, CXL-PK-03, and CXL-PK-06 (in which no acidification of samples was carried out), and prepared for sample analysis using either liquid-liquid extraction or dilution.

Table 32 summarizes the bioanalytical methods used to assess the concentrations of ceftazidime and avibactam.

Table 32. Summary of the bioanalytical methods used to assess the concentrations of ceftazidime and avibactam

No.	*Matrix*	*Analyte*	*LOQ (ng/mL)*	*Linear range (ng/mL)*	*Inter-assay bias (%)*	*Inter-assay CV (%)*	*Validation report*[a]	*Methods*	*Laboratory*
1	Plasma	Avibactam Ceftazidime	10.0 44.9	10.0 to 5000 44.9 to 2694	≤ ± 6.5 ≤ ± 1.9	≤ ± 12.1 ≤ ± 11.1	HFL100567/1	WMTD068	(b) (4)
2	Plasma	Avibactam	10.0 (low) 500 (high)	10.0 to 1000 500 to 50000	≤ ± 1.0 ≤ ± 9.6[b]	≤ ± 10.3 ≤ ± 5.8[c]	(b) (4) 10650-1	WMTD424, WMTD425, MWI0625, MWI0626	
3	Plasma	Avibactam	10.0	10.0 to 10000	≤ ± 5.7	≤ ± 12.3	8260799	HB-12-026	
4	Plasma	Avibactam	10.0	10.0 to 10000	≤ ± 11.0[b]	≤ ± 6.5[c]	8264-516	ABMHPP	
5	Plasma[d]	Avibactam	50.0	50.0 to 20000	≤ ± 1.1	≤ ± 8.1	PRD-RPT-BDM-00279	#308	Forest
6	Plasma[d]	Avibactam	50.0	50.0 to 50000	≤ ± 5.0	≤ ± 4.5	PRD-RPT-BDM-00404	#323	Forest
7	Plasma	Ceftazidime	43.7 (low) 437 (high) 437 (extended)	43.7 to 874 437 to 43700 437 to 87400	≤ ± 3.1 ≤ ± 2.2 ≤ ± 4.1	≤ ± 3.7 ≤ ± 5.9 ≤ ± 7.8	(b) (4) 11065 (b) (4) 01	WMTD432, WMTD433, MWI0642, MWI0643	(b) (4)
8	Plasma	Ceftazidime	43.8	43.8 to 87000	≤ ± 4.6	≤ ± 11.5	8260802	HB-12-024	
9	Plasma	Ceftazidime	43.8	43.8 to 87000	≤ ± 4.4[b]	≤ ± 4.4[c]	8264-521	CDEHPP	
10	Urine	Avibactam Ceftazidime	100 89.8	100 to 5000 89.8 to 2694	≤ ± 9.7 ≤ ± 5.0	≤ ± 8.1 ≤ ± 9.9	HFL100568/1	WMTD085	
11	Urine	Avibactam	500	500 to 300000	≤ ± 1.8	≤ ± 6.0	(b) (4) 11199 (b) (4) 02	MWI2565	
12	Urine	Avibactam	500	500 to 300000	≤ ± 2.4	≤ ± 9.4	8260798	HB-12-027	
13	Urine	Avibactam	500	500 to 300000	≤ ± 7.6[b]	≤ ± 5.0[c]	8264-519	ABMHPP	
14	Urine[d]	Avibactam	500	500 to 50000	≤ ± 1.4	≤ ± 4.6	PRD-RPT-BDM-00319	#312	Forest
15	Urine	Ceftazidime	437	437 to 262000	≤ ± 4.8	≤ ± 4.5	(b) (4) 111993 (b) (4) 02	MWI2564	(b) (4)
16	Urine	Ceftazidime	500	500 to 300000	≤ ± 5.4	≤ ± 11.8	8260801	HB-12-025	

Table 32. Continued

No.	*Matrix*	*Analyte*	*LOQ (ng/mL)*	*Linear range (ng/mL)*	*Inter-assay bias (%)*	*Inter-assay CV (%)*	*Validation report*[a]	*Methods*	*Laboratory*
17	Urine	Ceftazidime	435	435 to 262000	≤ ± 4.3	≤ ± 4.4	8264-522	CDEHUP	(b) (4)
18	Urine	Avibactam	500	500 to 200000	≤ ± 7.5	≤ ± 6.0	PRD-RPT-BDM-00583	#351	Forest
19	BAL	Avibactam	1.00 (lower) 10.0 (low) 500 (high)	1.00 to 400 10.0 to 1000 500 to 50000	≤ ± 6.3 ≤ ± 2.8 ≤ ± 2.7	≤ ± 12.5 ≤ ± 3.9 ≤ ± 5.8	(b) (4) 11041 (b) (4) 3	MW12636	(b) (4)
20	BAL	Ceftazidime	0.874 (lower) 43.7 (low) 437 (high)	0.874 to 437 43.7 to 874 437 to 87400	≤ ± 7.2 ≤ ± 4.6 ≤ ± 8.4	≤ ± 6.1 ≤ ± 5.7 ≤ ± 4.7	(b) (4) 110418 (b) (4) 2	MW12545	

2.6.4.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The assays were adequate to quantify CAZ and AVI concentrations over a clinically relevant range (Table 32). The linear ranges of each assay are also listed in Table 32. A calibration curve was generated using a quadratic regression with 1/concentration^2 weighting.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ and ULOQ of ceftazidime and avibactam for each assay were listed in Table 32.

2.6.4.3. What are the accuracy, precision, and selectivity at these limits?

Method validation and sample analysis supporting the clinical studies were conducted in accordance with approved standard operating procedures and according to Good Laboratory Practices guidelines. Intra- and inter-assay accuracy and precision of each method were evaluated by analyzing quality control (QC) plasma samples at defined concentrations, along with a calibration curve for quantification. Accuracy is expressed as percent bias (% deviation) of the concentration from its nominal concentration. Precision is expressed as percent coefficient of variation (%CV) of the mean concentration of the QC samples (Table 32).

For all assay methods, inter-assay %bias and inter-assay %CV within ±15% (±20% at the LLOQ). The reviewer finds that all analytical methods met the requirements for specificity, sensitivity, accuracy, and precision.

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The stability of avibactam and ceftazidime has been evaluated to determine the stability of the analytes in the study samples from the time of collection to the time of sample analysis, both in the main validations and in separate stability studies. From this work, appropriate solution stability of avibactam and ceftazidime in the analyte solutions has been demonstrated. The stability for avibactam and ceftazidime in plasma collected with sodium fluoride/potassium oxalate has been established at -20°C for at least 3 months and at -80°C for at least 12 months. The stability for avibactam in plasma collected with sodium fluoride/potassium oxalate has been established for at least 463 days at -70°C using freshly prepared standards on the day of analysis. The stability for avibactam in plasma collected with sodium fluoride/potassium oxalate with a phosphatase inhibitor cocktail has been established for 236 days at -70°C. Stability in urine has been established for at least 14 months at -80°C in acidified urine for avibactam and ceftazidime. Urine stability has also been established for 106 days at -70°C in non-acidified urine for avibactam. The stability of avibactam and ceftazidime in bronchoalveolar lavage fluid was also evaluated and established for at least 2 months at -80°C for avibactam and ceftazidime.

The short-term stability of ceftazidime spiked alone and in the presence of avibactam (8000 μg/mL) in human plasma has been successfully validated for three freeze/thaw cycles and six hours at room temperature.

The short-term stability of avibactam spiked alone and in the presence of ceftazidime in human plasma has been successfully validated for 24 hours at room temperature. Freeze/thaw stability of avibactam spiked alone and in the presence of ceftazidime in human plasma has been successfully validated for six freeze/thaw cycles.

2.6.4.5. What is the QC sample plan?

See Table 32. Low, medium, and high concentration QC samples were run in 2-6 replicates.

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4. Appendix

4.1. Pharmcometrics Review

1. SUMMARY OF FINDINGS

The population pharmacokinetic (PK) models developed by the Applicant are able to characterize the pharmacokinetics of ceftazidime (CAZ) and avibactam (AVI), respectively, based on the combined dataset from 10 Phase I and 2 Phase II studies in healthy volunteers (HV) and patients with complicated Intro-Abdominal Infection (cIAI) or complicated Urinary Tract Infection (cUTI).

The Applicant's population PK analysis of CAZ included a total of 3619 observations from 216 (74 Phase I and 142 Phase II) subjects including 74 (34.3%) HV, 58 (26.9%) cUTI patients, and 84 (38.9%) cIAI patients. CAZ concentrations were well described by a two-compartment intravenous (IV) infusion model with first-order elimination. Population effects (HV versus cIAI versus cUTI) were included *a priori* on clearance (CL) and apparent volume of the control compartment (V1) in the base model. Since CAZ CL is predominantly renal, an effect of creatinine clearance (CrCL) on CL was included in the base model by leveraging literature data in addition to the population effects on CL and V1. Race (Japanese versus non-Japanese versus non-Asian) was significant covariate on both CL and V1, while body weight only had effect on V1. The following population PK estimates (%RSE) of CAZ were obtained: CL 7.31 L/h (2.92%); V1 10.8 L (4.68%); inter-compartmental clearance (Q) 7.72 L/h (11.7%); and apparent volume of the peripheral compartment (V2) 6.83 L (4.48%). The inter-subject variability was 27.8% (21.1%) for CL; 37.1% (30.7%) for V1; and 18.3% (31.9%) for V2 in Phase I only.

For the AVI, the population PK analysis, dataset included 475 subjects with 8124 observations, including 7469 observations from 333 HV (70%) in 10 Phase I clinical studies and 655 observations (260 and 395, for the cIAI and cUTI studies, respectively) from 58 (12.2%) cIAI patients and 84 (17.7%) cUTI patients in the two Phase II clinical studies. AVI concentration data were well described by a two-compartment IV infusion model with first-order elimination. Population effects (HV versus cIAI versus cUTI) were included in the based model prior to evaluating the remaining covariates. Consistent with the primarily renal clearance of AVI, CrCL was the primary predictor of CL. Renal function category (Augmented renal clearance (ARC) and end-stage renal disease (ESRD)) and body weight were significant covariates on V1. Estimates of population PK parameters were 10.9 L/h (1.93%), 12.7 L (1.87%), 6 L/h (6.45%), and 7.46 L (3.05%) for CL, V1, Q, and V2, respectively. Estimates (%RSE) of inter-individual variability in the final population PK model were relatively small at 21.9% (15%), 28.8% (19.5%), and 21.4% (32%) for CL, V1, and V2, respectively.

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 Is the dose adjustment for CAZ and AVI based on renal impairment appropriate?

Yes. CrCL was significant covariate on CL for both CAZ and AVI in the final population PK model (Figure 1 and 2). Unlike AVI, the CAZ dataset contained no dedicated Phase I studies in subjects with renal impairment. Only 4 subjects in the Phase II studies were recorded as having moderate renal impairment,

based on the Cockcroft-Gault CrCL at baseline. The relationship between CL and CrCL over the full range of renal function (from ESRD to normal function) was derived by adding historical literature data for CAZ treatment in subject with CrCL<50 mL/min to augment the population PK data. The relationship between CrCL and CL was characterized by a piecewise relationship. While the cut point for the CAZ relationship was 100 mL/min, the cut point for AVI was identified as 80 mL/min corresponding to the demarcation between patients with normal and mild renal function as assessed using the Cockcroft-Gault function.

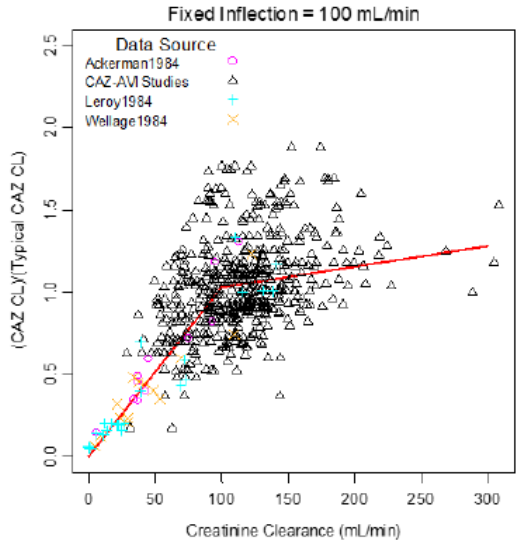


Figure 1 Fit of the CrCL regression model including literature data for CAZ.

Adopted from sponsor's population pharmacokinetics report, Figure 9.

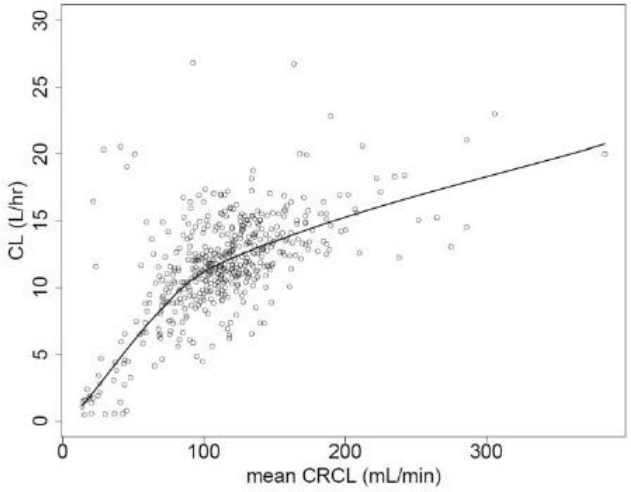


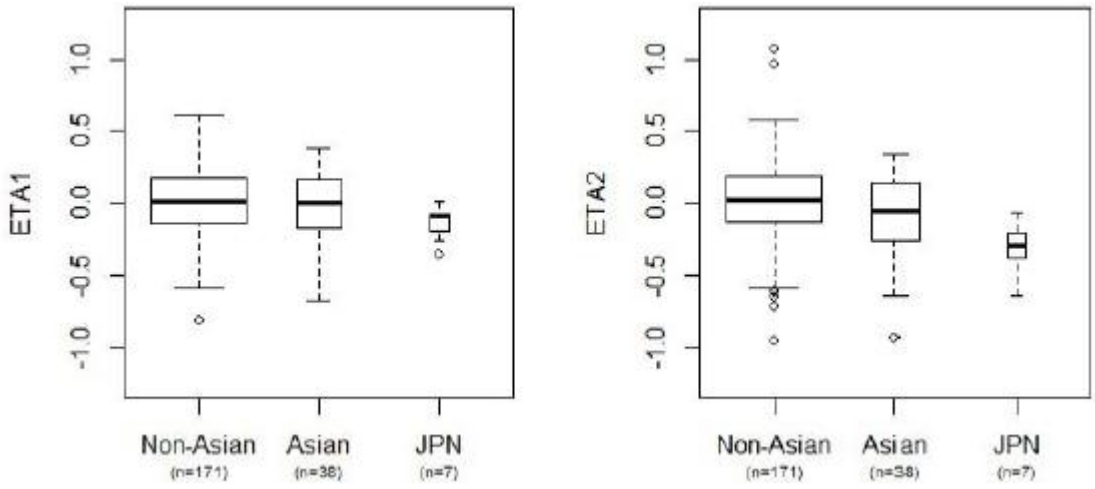
Figure 2 Individual posthoc estimates of clearance versus mean CrCL for the final base model of AVI

Adopted from sponsor's population pharmacokinetics report, Figure 17.

In addition to renal impairment, body weight was also identified as a significant covariate on V1 for CAZ and AVI. Race (Japanese versus non-Japanese Asian versus non-Asian) was significant covariates on CL and V1 for CAZ (Figure 3). However, no dose adjustments are recommended based on these intrinsic factors as the impact of these factors on CAZ and AVI exposure were less than 20% and deemed not to be of clinical relevance. In general agreement with the current product labeling for CAZ, initial Phase I/II trials of CAZ-AVI and AVI alone have suggested that CAZ-AVI exposure increases with increasing severity of renal impairment. Therefore, dose adjustments may be required in subjects with moderate or severe renal impairment.

The proposed dose and dosing regimen was as follows:

- CrCL >50 mL/min: 2500 mg (2000 mg ceftazidime + 500 mg avibactam) infused q8h over 2 hours
- 31 mL/min ≤ CrCL ≤ 50 mL/min: 1250 mg (1000 mg ceftazidime + 250 mg avibactam) infused every 12 hours over 2 hours
- 16 mL/min ≤ CrCL ≤ 30 mL/min: 1250 mg (1000 mg ceftazidime + 250 mg avibactam) infused every 24 hours over 2 hours
- 6 mL/min ≤ CrCL ≤ 15 mL/min: 625 mg (500 mg ceftazidime + 125 mg avibactam) infused every 24 hours over 2 hours
- CrCL ≤ 5 mL/min: 625 mg (500 mg ceftazidime + 125 mg avibactam) infused every 48 hours over 2 hours



- **Figure 3 Individual estimates of η_{CL} (ETA1) and η_{V1} (ETA2) stratified by race for CAZ.**

Adopted from sponsor's population pharmacokinetics report, Figure 10.

1.1.2 Is the proposed breakpoint based on probability of target attainment (PTA) appropriate?

Yes. Given the limited data available for analysis from the Phase II studies, formal exposure-response modeling was not feasible. Instead, predefined preclinical targets were used in subsequent PTA simulations.

- T1: 40% *f*T >MIC for CAZ and 40% *f*T >CT of 0.5 mg/L for AVI

- T2: 50% *f*T >MIC for CAZ and 50% *f*T >CT of 0.5 mg/L for AVI
- T3: 40% *f*T >MIC for CAZ and 40% *f*T >CT of 1.0 mg/L for AVI
- T4: 50% *f*T >MIC for CAZ and 50% *f*T >CT of 1.0 mg/L for AVI

Based on the 5000 simulated PK profiles with 2 hour infusion duration, joint attainment of target exposures for CAZ and AVI was assessed for the treatment regimens and targets (labeled T1 through T4). For each MIC, the six renal function/dose regimen combinations simulated were summarized as the percent of subjects meeting each potential target as summarized in Table 1 and 2.

Table 1 Summary of joint target attainment for MICs from 1 mg.mL to 32 mg/mL for cIAI population

MIC (mg/L)	Renal Function Group	Dose Regimen	T1	T2	T3	T4
1	1. Normal	2000 mg CAZ+500 mg AVI q8h	100	100	100	98.9
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	99.9
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	100	100	99.9	98.9
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	100	99.9	99.8	97.8
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	100	100	100	100
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	100	100	100
2	1. Normal	2000 mg CAZ+500 mg AVI q8h	100	100	100	98.9
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	99.9
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	100	100	99.9	98.9
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	100	99.9	99.8	97.8
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	100	100	100	100
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	100	100	100
4	1. Normal	2000 mg CAZ+500 mg AVI q8h	100	100	100	98.9
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	99.9
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	100	100	99.9	98.9
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	100	99.8	99.8	97.8
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	100	100	100	100
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	100	100	100
8	1. Normal	2000 mg CAZ+500 mg AVI q8h	99.8	98.3	99.8	98.1
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	99.9
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	98.8	95.7	98.8	95.7
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	95.5	85.9	95.5	85.9
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	97.3	94.4	97.3	94.4
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	99.9	100	99.9
16	1. Normal	2000 mg CAZ+500 mg AVI q8h	75.4	50.8	75.4	50.8
	2. Mild	2000 mg CAZ+500 mg AVI q8h	98.1	93.8	98.1	93.8
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	50.1	35.2	50.1	35.2
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	35.0	21.8	35.0	21.8
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	47.5	40.8	47.5	40.8
	6. ESRD	500 mg CAZ+125 mg AVI q48h	88.2	84.7	88.2	84.7
32	1. Normal	2000 mg CAZ+500 mg AVI q8h	5.1	1.3	5.1	1.3
	2. Mild	2000 mg CAZ+500 mg AVI q8h	41.3	27.5	41.3	27.5
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	1.2	0.4	1.2	0.4
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	0.7	0.3	0.7	0.3
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	3.3	2.3	3.3	2.3
	6. ESRD	500 mg CAZ+125 mg AVI q48h	39.1	36.8	39.1	36.8

Adopted from sponsor's population pharmacokinetics report, Table 10 .

In simulations based on the final CAZ and AVI PK models, at MICs of less than 8 mg/L, all renal function categories achieved almost 100% joint target attainment for the potential targets T1 through T4. At an MIC of 8 mg/L, the "Severe 1" (Severe 1: 16 mL/min≤CrCL≤30 mL/min; Severe 2: 6 mL/min≤CrCL≤15 mL/min) group achieved greater than 90% joint target attainment for T1 and T3, and 85-86% target attainment for T2 and T4 (Table 1 and 2). Overall, the simulation results support a pharmacokinetic/pharmacodynamic (PK/PD) breakpoint of 8 mg/L across renal function groups with the dose adjustments described.

Table 2 Summary of joint target attainment for MICs from 1 mg.mL to 32 mg/mL for cUTI population

MIC (mg/L)	Renal Function Group	Dose Regimen	T1	T2	T3	T4
1	1. Normal	2000 mg CAZ+500 mg AVI q8h	100	100	100	99.7
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	100
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	100	100	100	99.9
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	100	100	100	99.7
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	100	100	100	100
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	100	100	100
2	1. Normal	2000 mg CAZ+500 mg AVI q8h	100	100	100	99.7
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	100
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	100	100	100	99.9
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	100	100	100	99.7
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	100	100	100	100
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	100	100	100
4	1. Normal	2000 mg CAZ+500 mg AVI q8h	100	100	100	99.7
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	100
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	100	100	100	99.9
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	100	100	100	99.7
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	100	100	100	100
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	100	100	100
8	1. Normal	2000 mg CAZ+500 mg AVI q8h	100	99.9	100	99.7
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	100	100	100
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	100	99.9	100	99.9
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	99.9	98.8	99.9	98.8
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	100	99.8	100	99.8
	6. ESRD	500 mg CAZ+125 mg AVI q48h	100	100	100	100
16	1. Normal	2000 mg CAZ+500 mg AVI q8h	98.2	90.0	98.2	90.0
	2. Mild	2000 mg CAZ+500 mg AVI q8h	100	99.8	100	99.8
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	92.3	82.4	92.3	82.4
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	82.0	65.6	82.0	65.6
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	86.1	80.2	86.1	80.2
	6. ESRD	500 mg CAZ+125 mg AVI q48h	99.2	98.5	99.2	98.5
32	1. Normal	2000 mg CAZ+500 mg AVI q8h	38.3	19.9	38.3	19.9
	2. Mild	2000 mg CAZ+500 mg AVI q8h	88.4	76.8	88.4	76.8
	3. Moderate	1000 mg CAZ+250 mg AVI q12h	20.8	12.7	20.8	12.7
	4. Severe 1	1000 mg CAZ+250 mg AVI q24h	12.9	7.2	12.9	7.2
	5. Severe 2	500 mg CAZ+125 mg AVI q24h	23.5	19.3	23.5	19.3
	6. ESRD	500 mg CAZ+125 mg AVI q48h	70.3	66.4	70.3	66.4

Adopted from sponsor's population pharmacokinetics report, Appendix 16.2.

2 PERTINENT REGULATORY BACKGROUND

Ceftazidime-avibactam (CAZ-AVI) is being developed by Cerexa, Inc. in collaboration of AstraZeneca for the treatment of infections caused by susceptible gram-negative pathogens, including pathogens with multi-drug resistance (MDR). CAZ is a bactericidal β-lactam and AVI is a β-lactamase inhibitor that has a spectrum of activity against Ambler class A ESBLs, class A KPCs, class C (AmpC) enzymes, and some class D enzymes. Unlike currently available β-lactamase inhibitors, AVI does not induce β-lactamase production. AVI has no meaningful antibacterial activity at potentially achievable concentrations in humans.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK analysis

3.1.1 Objectives:

1. To develop population PK models for IV administration of both CAZ and AVI that describes the plasma concentration-time relationship and can be used to provide individual predicted exposure metrics.
2. To evaluate the impact of covariates of interest, including body weight/size, age, gender, race, measures of kidney function (including ARC and ESRD on and off dialysis for AVI), and disease status (i.e., healthy subjects in Phase I studies versus cIAI patients versus cUTI patients).
3. To examine the potential relationship between exposure metrics and microbiological response in each of the two CAZ-AVI Phase II studies to determine if a PK/PD index (breakpoint) can be defined.
4. To perform model-based simulations to predict probability of PK/PD target attainment (PTA) for treatment regimens and assess the potential need for dose adjustments based on identified covariates, as well as levels of renal impairment from mild to end-stage renal disease.

3.1.2 Study included in the population PK model

The data used to develop the population PK model of CAZ were obtained from 4 Phase I (NXL104-1001, NXL104-1002, NXL105/2001, and NXL104/2002), and 2 Phase II studies (D4280C00010 and D4280C00011). There were 74 (34.3%) HV, 58 (26.9%) cUTI patients, and 84 (38.9%) cIAI patients. The majority of the subjects were Caucasian (59.7%). The median age of the subjects was 35 years old (range, 18-83), 31.9% were females, and the median CrCL was 115 mL/min (range, 40.9-274). Figure 4 displays observed CAZ concentrations versus time after dose for all subjects.

The population PK analysis data of AVI included 10 Phase I (NXL104-1001, NXL104-1002, NXL104/1003, NXL104/1004, NXL105/2001, NXL104/2002, CXL-PK-01, CXL-PK-03, CXL-PK-04, and CXL-PK-06) and 2 Phase II studies (D4280C00010 and D4280C00011). The observed AVI concentrations versus time after dose for all subjects are shown in Figure 5. There were 333 (70%) HV, 58 (12.2%) cUTI patients, and 84 (17.7%) cIAI patients. The majority of the subjects were Caucasian (64%). The median age was 34 years (range, 18-83), 29.7% were females, and the median CrCL was 113 mL/min (range, 14-384 mL/min). Because the AVI dataset included a renal insufficiency study (NXL104/1003) and a study including HV with severely impaired renal function (CXL-PK-03), AVI PK in subjects with renal impairment was characterized based solely on the available population PK data.

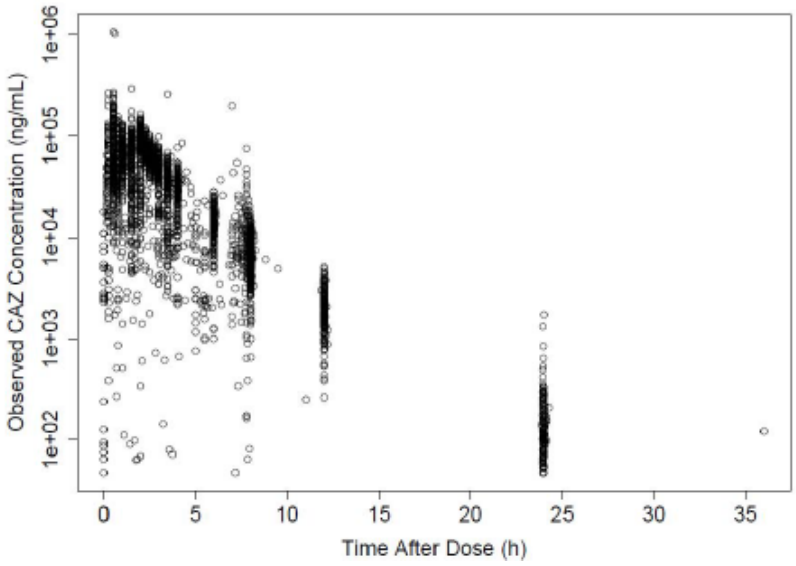


Figure 4 Observed CAZ concentration (log scale) versus time after dose for all subjects.

Adopted from sponsor's population pharmacokinetics report, Figure 1.

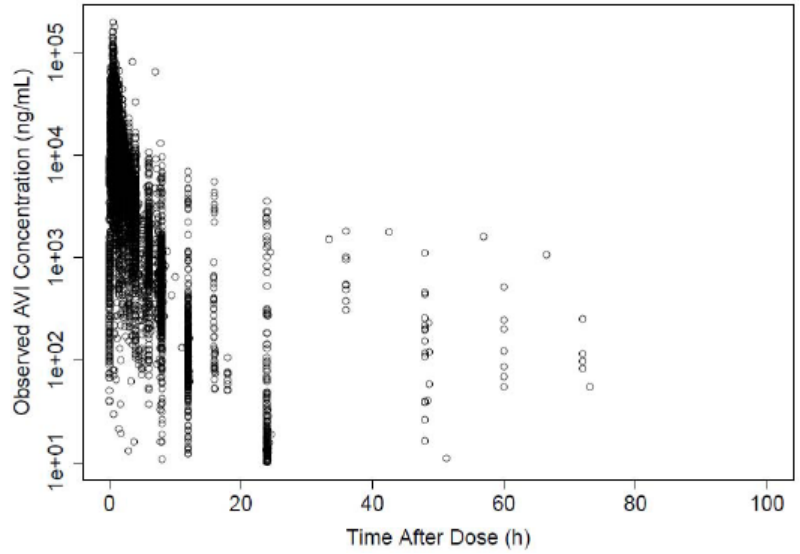


Figure 5 Observed AVI concentration (log scale) versus time after dose for all subjects.

Adopted from sponsor's population pharmacokinetics report, Figure 13.

3.1.3 Base model:

The CAZ data were well described by a two-compartment IV infusion model with first order elimination. Graphical exploration of individual post hoc parameter estimates stratified by population and other covariates of interest suggested that population effects have a larger impact on PK parameters than the demographic factors considered. Also, differences between HV and Phase II patients were more pronounced for V1 than CL. Therefore, population effects (HV versus cUTI versus cIAI) were included *a*

priori on CL and V1 in the base model. Since CAZ clearance is predominantly renal, an effect of CrCL on CL was included in the base model in addition to the population effects on CL and V1. However, the available CAZ dataset lacked data for subjects with severe renal impairment; all subjects in the dataset had mild or moderate impairment, or normal renal function. To extrapolate to a lower range of renal function, individual estimates of CL from the literature were incorporated in the base PK model prior to covariate model building as shown in Figure 1.

The PK of AVI following IV dose administration was best described by a two-compartment IV infusion model with first-order elimination. Population effects were included prior to evaluating the remaining covariates because confounded covariates across the populations would likely impact the significance of covariate effect. Additionally, "hockey-stick" relationship was observed between CL and CrCL. Thus, the effect of CrCL on CL was also included in the final base model prior to investigation of the remaining covariates. Ultimately, the effect was best described by a model combining a power function for CrCL<80 mL/min and a linear fit for CrCL⩾80 mL/min. In addition, an effect of ARC was estimated on the slope of the relationship for CrCL⩾80 mL/min (Figure 2).

3.1.4 Covariate model development

Potential covariate-parameter relationships were explored by inspection of plots of individual random effects for CL and V1 estimated from the CAZ base model versus covariates of interest. In the forward search, effects of weight on V1 (ΔOFV -16.9), race (Japanese versus non-Japanese Asian versus non-Asian) on VI (ΔOFV -20.6) and race (Japanese versus non-Japanese) on CL (ΔOFV -23.4) were added to the model with P<0.01. The final CAZ population PK model includes the following parameter-covariate relationship:

$$CL_{CRCL} = \begin{cases} 0.0103 \cdot CRCL, & CrCL < 100 \\ 0.0103 * 100 + 0.00125 \cdot (CRCL - 100), & CrCL \geq 100 \end{cases}$$

$$CL_i = \theta_1 \cdot CL_{CRCL} \cdot (1 + \theta_9 \cdot Asian) \cdot (1 + \theta_{10} \cdot Japanese) \cdot \theta_5^{cIAI} \cdot \exp(\eta_{CL,i})$$

$$V1_i = \theta_2 \cdot \theta_6^{cUIT} \cdot \theta_7^{cIAI} \cdot (1 + \theta_{11} \cdot Japanese) \cdot \left(\frac{WT}{74.4}\right)^{\theta_8} \cdot \exp(\eta_{V1,i})$$

$$Q_i = \theta_3 \cdot \exp(\eta_{Q,i})$$

$$V2_i = \theta_4 \cdot \exp(\eta_{V2,i}{}^{Phase\ I})$$

In the model above, Asian is an indicator variable with value "1" for non-Japanese Asian subjects and "0" for all other subjects. Japanese is an indicator variable with value "1" for Japanese subjects and "0" for all other subjects. Likewise, cIAI, cUTI, and Phase I are indicator variables with value "1" for the indicated population and "0" for all other subjects.

The graphical evaluation of correlations between the individual posthoc estimates and the remaining covariates of interest revealed that the following covariates effects were added to the AVI population PK model with p<0.01, in the order listed: weight on V1 (ΔOFV -179) and ARC on V1 (ΔOFV -16.3). The final AVI population PK model includes the following parameter-covariate relationships:

$$CL_{CRCL} = \begin{cases} (CRCL/80)^{\theta_7}, & CrCL < 80 \\ 1 + \theta_8 \cdot {\theta_{13}}^{ARC} \cdot (CRCL - 80), & CrCL \geq 80 \end{cases}$$

$$CL_i = \begin{Bmatrix} \theta_1 \cdot {\theta_5}^{ESRD} \cdot (1 + \theta_9 \cdot cIAI) \cdot CL_{CRCL}, & off\ dialysis \\ \theta_6, & on\ dialysis \end{Bmatrix} \cdot \exp(\eta_{CL,i})$$

$$V1_i = \theta_2 \cdot (1 + \theta_{11} \cdot cUTI) \cdot (1 + \theta_{12} \cdot cIAI) \cdot (1 + \theta_{15} \cdot ARC) \cdot \left(\frac{WT}{74}\right)^{\theta_{17}} \cdot \exp(\eta_{V1,i})$$

$$Q_i = \theta_3 \cdot \exp(\eta_{Q,i})$$

$$V2_i = \theta_4 \cdot \exp(\eta_{V2,i})$$

In the model above, ARC is an indicator variable with value “1” for subjects with ARC and “0” for all other subjects. ESRD is an indicator variable with value “1” for ESRD subjects off dialysis and “0” for all other subjects. Likewise, cIAI and cUTI are indicator variables with value “1” for the indicated population and “0” for all other subjects.

3.1.5 Final population model

The final CAZ population PK model parameter estimates are presented in Table 3. CL estimates for both HV and cUTI patients were similar, but were 54% higher for cIAI patients. cUTI and cIAI patients were found to have larger V1 than HV, 18.5 L (71.4%) and 29.5 L (173%), respectively. Japanese subjects had 22.9% lower CL than non-Asians and 32.3% lower V1 than non-Asians/non-Japanese Asians. Non-Japanese Asians had 16.1% lower CL than non-Asians. Subjects with a larger body weight were estimated to have higher V1. Subjects at the lower (10th percentile, 53 kg) and upper (90th percentile, 93 kg) extremes of the observed weight range were predicted to have 20% lower or 16% higher V1, respectively, than subjects of median weight (74.4 kg).

Parameter estimates for the final AVI Population PK model are provided in Table 4. The estimated CL for a typical HV or cUTI subject was 10.9 L/h. Estimated CL for cIAI subjects was 40.1% higher at 15.3 L/h. For ESRD subjects on dialysis, CL was 18.7 L/h. For subjects with ARC, the increase in CL at the 90th percentile of CrCL was greater than for non-ARC subjects, with a 40.4% increase in CL over the typical value. The typical V1 was 12.7 L for HV (reference), 32 L for cIAI subjects (152% higher than HS), and 21.8 L for cUTI subjects (71.6% higher than HS). V1 was also 38.1% higher in subjects with ARC (17.5 L). Changes in body weight were found to have a nearly proportional effect on V1, with a 10% decrease or increase in weight resulting in about an 11% decrease or increase in V1, respectively.

Table 3 Parameter estimates for the final CAZ Population PK model.

	Parameter (units)	Point Estimate	%RSE	Inter-Individual Variability (CV%)[3]
	Regression Estimates of CrCL effect on CL CrCL<100 mL/min: slope1*CrCL CrCL≥100 mL/min: slope1*100 + slope2*(CrCL-100)			
	slope1	0.0103036	0.409	--
	slope2	0.001252	8.84	--
	NONMEM Model Estimates			
θ_1	CL (L/h)[1]	7.31	2.92	27.8
θ_2	V1 (L)	10.8	4.68	
θ_3	Q (L/h)	7.72	11.7	37.1
θ_4	V2 (L)	6.83	4.48	18.3 (PH1)
θ_5	Population Effect on CL (cIAI), CL*θ_5	1.54	5.72	
θ_6	Population Effect on V1 (cUTI), V1*θ_6	1.71	15.7	
θ_7	Population Effect on V1 (cIAI), V1*θ_7	2.73	11.0	
θ_8	WT Effect on V1[2], $(WT/74.44)^{\theta_8}$	0.66	36.0	
θ_9	Race Effect on CL (non-JPN Asian)	-0.161	34.4	
θ_{10}	Race Effect on CL (JPN)	-0.229	18.4	
θ_{11}	Race Effect on V1 (JPN)	-0.323	21.0	
				Shrinkage (%)
ηCL	etaCL	0.0773	21.1	12.3
	ηCL-ηV1 covariance[1]	0.0654	36.3	
ηV1	etaV1	0.137	30.7	24.8
ηV2	etaV2, Phase 1 only	0.0334	31.9	53.0
	Additive Error, Phase 1	203000	64.2[4]	3.04
	Proportional Error, Phase 1	0.0342	24	3.04
	Additive Error, Phase 2	428000	168[4]	6.81
	Proportional Error, Phase 2	0.276	9.41	6.81

Data Source: run2BFin.mod
Abbreviations: CL, central clearance (L/h); V1, central volume (L); Q, Inter-compartmental clearance (L/h); V2, peripheral volume (L); WT, body weight (kg); JPN, Japanese
[3]Correlation Coefficient (r) between random effects of CL and V1 = 0.64.
[4]High %RSE for Phase 1 additive error and Phase 2 additive error indicate these terms were poorly estimated in the NONMEM fit; however, the estimates were within the nonparametric bootstrapped 95% CI and the bootstrap CI does not include zero; hence, the terms were retained in the model.

Adopted from sponsor's population pharmacokinetics report, Table 4.

Table 4 Parameter estimates for the final AVI Population PK model.

	Parameter	Estimate	%RSE	Inter-Individual Variability (CV%)
θ_1	CL (L/h)	10.9	1.93	21.9
θ_7	CL, $(CRCL/80)^{\theta 7}$, CrCL<80 mL/min	1.25	4.79	
θ_8	CL, $(1+\theta_8*(CRCL-80))$, CrCL≥80 mL/min	0.00198	18.3	
θ_{10}	Population Effect on CL (cIAI), $CL*(1+\theta_{10})$	0.401	31.3	
θ_{13}	ARC effect on slope of CrCL≥80 mL/min effect on CL, $\theta_8*\theta_{13}$	2.37	18.6	
θ_5	ESRD effect on CL, $CL*\theta_5$	0.0551	27.3	
θ_6	CL, estimate for dialysis subjects	18.7	9.15	
θ_2	V1 (L)	12.7	1.87	28.8
θ_{17}	V1, $(WT/74)^{\theta 17}$	1.11	8.83	
θ_{12}	Population Effect on V1 (cIAI), $V1*(1+\theta_{12})$	1.52	30.6	
θ_{11}	Population Effect on V1 (cUTI), $V1*(1+\theta_{11})$	0.716	43.7	
θ_{15}	ARC effect on V1, $V1*(1+\theta_{15})$	0.381	27.8	
θ_3	Q (L/h)	6	6.45	
θ_4	V2 (L)	7.46	3.05	21.4
				Shrinkage (%)
ηCL	etaCL	0.0479	15	7.83
ηV1	etaV1	0.0831	19.5	16.8
ηV2	etaV2	0.0456	32	30.1
	Additive Error, Phase 1[1]	1070	30.7	5.44
	Proportional Error, Phase 1	0.0333	15.9	5.44
	Proportional Error, Phase 2	0.416	21	4.80

Data Source: runFM03.mod; Abbreviations: CL, central clearance (L/h); V1, central volume (L); Q, Inter-compartmental clearance (L/h); V2, peripheral volume (L); WT, body weight (kg); IIV, inter-individual variability.
[1]Reported as variance.

Adopted from sponsor's population pharmacokinetics report, Table 6.

3.1.6 Model evaluation

The nonparametric bootstrap of the final model of CAZ was performed. NONMEM and bootstrap estimates were similar and confidence intervals were in close agreement for all parameters for CAZ.

The final model of CAZ was also evaluated by visual predictive check (VPC). The VPC is stratified by patients population (HV, cUTI, cIAI), and plotted versus time since last dose (<25 h) (Figure 6). The model describes the observed data well, and model predictions are within the 90% prediction intervals.

The nonparametric bootstrap of the final model of AVI was executed. NONMEM and bootstrap estimates were very similar, with confidence intervals typically in close agreement.

The final model of AVI was also evaluated by VPC. The VPC in Figure 7 is stratified by patient population (HV, cUTI, cIAI), and plotted versus time since last dose (≤25 h). The model describes the observed data well, and model predictions are within the 90% prediction intervals.

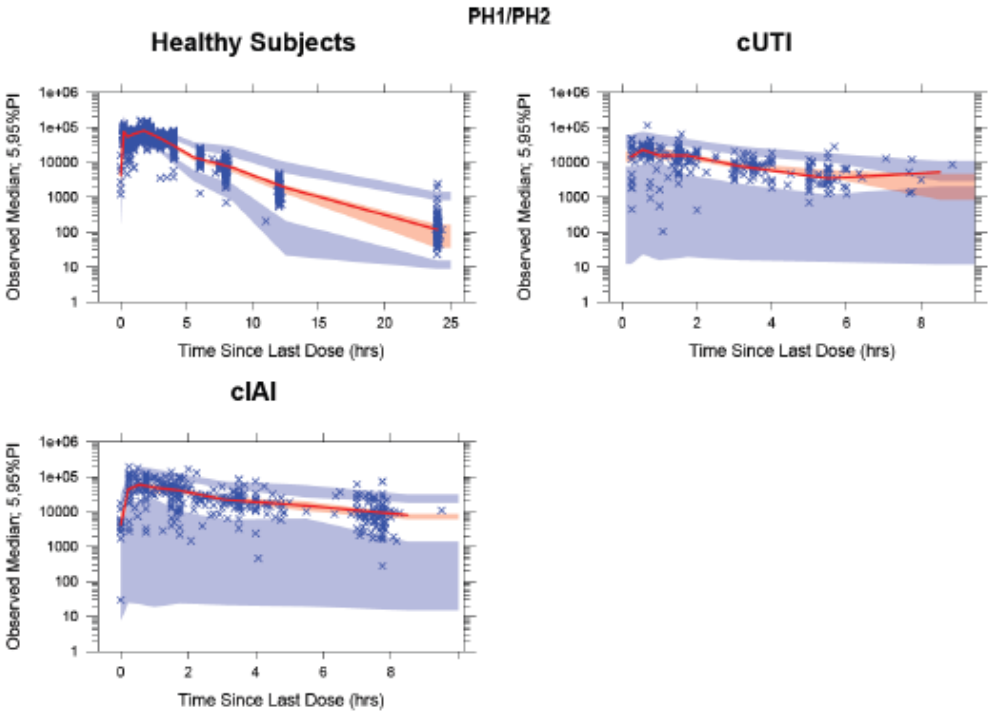


Figure 6 Visual Predictive Check for CAZ Stratified by Population.

Adopted from sponsor's population pharmacokinetics report, Figure 11.

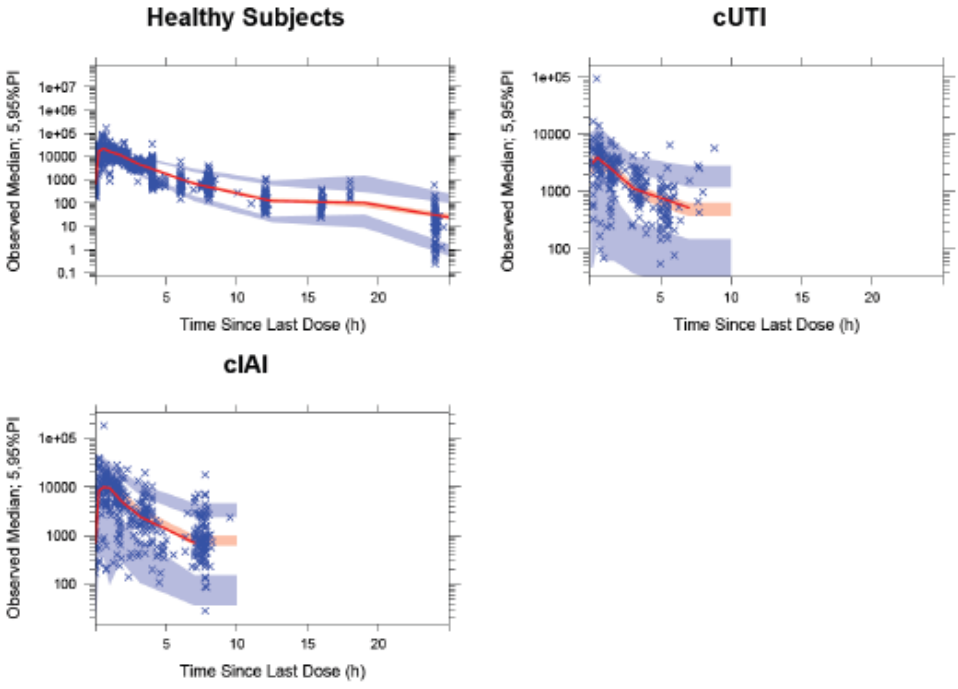


Figure 7 Visual Predictive Check for AVI Stratified by Population.

Adopted from sponsor's population pharmacokinetics report, Figure 20.

Reviewer's comment: The reviewer verified the sponsor's population PK analyses for CAZ and AVI. The goodness-of-fit plots indicate that the model reasonably describes the data. The reviewer agrees that dose adjustment should be made based on renal function using CrCL.

3.2 Exploratory analysis of exposure-response

Relationships between simulated CAZ-AVI exposure measures of interest and microbiologic response were evaluated through exploratory plots of individual data from the 2 Phase II studies (NXL104/2001 for the cUTI population and NXL104/2002 for the cIAI population). Exposure measures included fraction of the inter-dose time interval (%*f*T) during which a patient's free drug concentration remained above the highest baseline MIC for each subject for CAZ and thresholds of 0.5 and 1 mg/L for AVI. Results were summarized as histograms of CAZ %*f*T >MIC, AVI %*f*T >0.5 mg/L, and AVI %*f*T >1.0 mg/L stratified by microbiologic outcome status (favorable versus unfavorable).

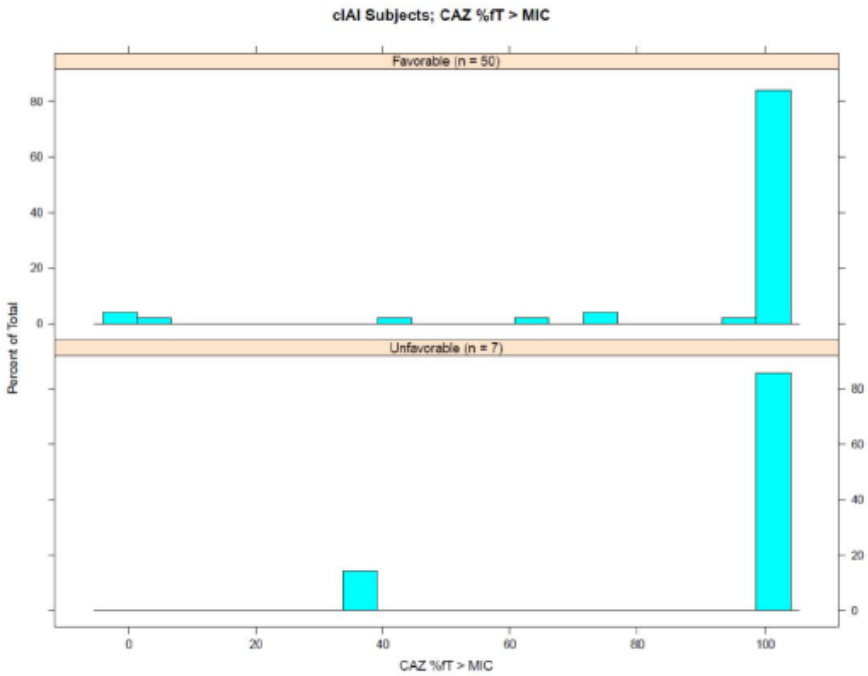


Figure 8 Histogram of CAZ%*f*T>MIC stratified by microbiological outcome status for cIAI population

Adopted from sponsor's population pharmacokinetics report, Figure 23.

Results of the exploratory analyses for the cIAI population show that almost all CAZ %*f*T >MIC values were close to 100% and unfavorable microbiologic outcomes were relatively infrequent (Figure 8). Similar results could be found if stratified by AVI %*f*T >0.5 mg/L and AVI %*f*T >1.0 mg/L.

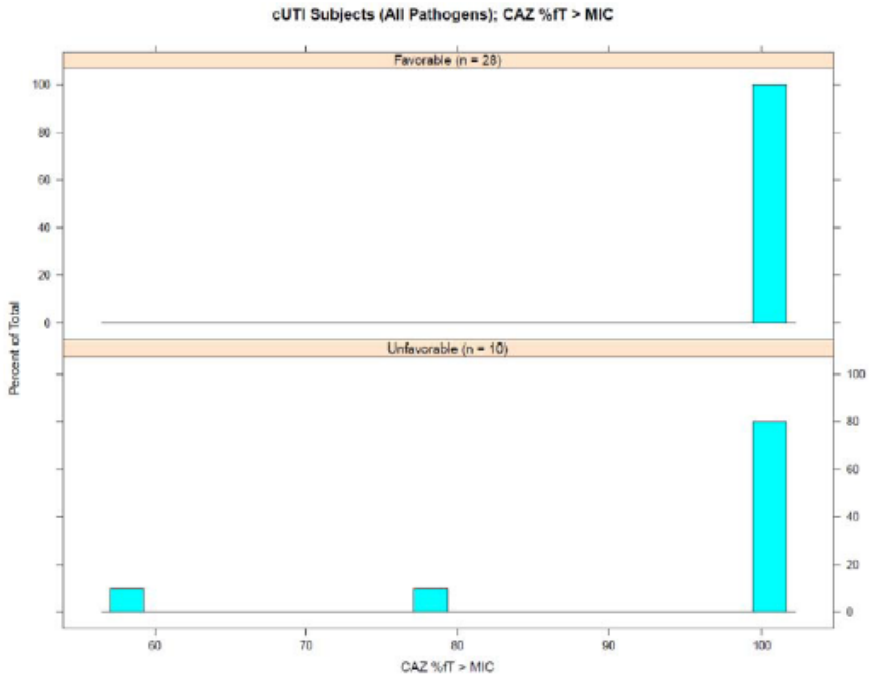


Figure 9 Histogram of CAZ%*f*T>MIC stratified by microbiological outcome status for cUTI population

Adopted from sponsor's population pharmacokinetics report, Figure 27

Similar to cIAI population, almost all CAZ %*f*T>MIC values were close to 100% for favorable and unfavorable microbiologic outcomes in the cUTI population for all baseline pathogens stratified by CAZ %*f*T >MIC (Figure 9).

3.3 Model application

3.3.1 Prediction of exposure in patients with renal impairment

Steady-state PK profiles for CAZ and AVI were characterized by simulating 100 observations per subject, evenly spaced across the dosing interval. Exposure metrics (AUC and Cmax) based on a 2 hour infusion duration are summarized in Table 3 and 4 for 5000 simulated cIAI and cUTI patients. Simulations were completed for each renal function group. Table 5 and 6 shows the exposure metrics under different doses and dosing regimens for normal and mild renal function groups. These scenarios were evaluated as updated information from the Applicant suggests that a subset of patients with moderate renal function may have had on-treatment increases in renal function (to mild or normal renal function) but no alteration to the administered dose. As such, these simulation scenarios provide an assessment of the PTA where patients are initiated on a reduced dose based on renal function, but subsequently have improvements in renal function without an accompanying dose adjustment.

Table 3 Summary of Simulated PK exposure Metrics for cIAI population (originally proposed CAZ/AVI doses in the label based on renal function)

Renal Function & Treatment	PK Parameter*	Mean	SD	Median	Geom. Mean	Geom. CV	Min	Max
1. Normal 2000 mg CAZ+500 mg AVI q8h	AVI Cmax	9.31	1.87	9.17	9.13	61.9	3.46	18.5
	AVI Total Daily AUCss	93.5	21.3	91.2	91.1	62.2	36.1	216
	CAZ Cmax	47.2	13.4	45.5	45.4	63.1	11.4	119
	CAZ Total Daily AUCss	542	161	518	519	63.3	167	1480
2. Mild 2000 mg CAZ+500 mg AVI q8h	AVI Cmax	11.2	2.37	11	11	62	4.23	21.9
	AVI Total Daily AUCss	131	36.4	126	127	62.9	49.2	337
	CAZ Cmax	59.9	17.1	57.6	57.6	63.1	17.7	154
	CAZ Total Daily AUCss	828	260	783	790	63.6	253	2490
3. Moderate 1000 mg CAZ+250 mg AVI q12h	AVI Cmax	6.84	1.48	6.72	6.68	62.1	2.61	13.7
	AVI Total Daily AUCss	80.3	22.8	76.8	77.2	63	31.9	198
	CAZ Cmax	33.5	9.6	32.3	32.1	63.2	10.1	90
	CAZ Total Daily AUCss	448	142	425	427	63.6	155	1350
4. Severe 1 1000 mg CAZ+250 mg AVI q24h	AVI Cmax	7.61	1.85	7.44	7.39	62.5	2.77	15.9
	AVI Total Daily AUCss	82.8	26.7	78	78.8	63.7	30.6	236
	CAZ Cmax	33.9	10.2	32.5	32.5	63.4	9.37	83.2
	CAZ Total Daily AUCss	400	136	377	378	64	126	1310
5. Severe 2 500 mg CAZ+125 mg AVI q24h	AVI Cmax	6.79	2.07	6.41	6.5	63.4	2.52	19.3
	AVI Total Daily AUCss	116	47.6	106	108	65.5	36.9	391
	CAZ Cmax	27	9.03	25.6	25.7	63.9	8.26	89.1
	CAZ Total Daily AUCss	455	180	419	423	65.2	136	1620
6. ESRD 500 mg CAZ+125 mg AVI q48h	AVI Cmax	5.26	1.04	5.16	5.16	61.9	2	10.1
	AVI Total Daily AUCss	75.6	16.8	73.6	73.8	62.1	32.9	170
	CAZ Cmax	45.7	22.9	39.5	41.2	67	11.6	250
	CAZ Total Daily AUCss	898	527	736	780	69.4	186	5650

*For AVI and CAZ, Cmax is reported in mg/L and AUCss is reported in mg*h/mL.

Adopted from sponsor's population pharmacokinetics report, Table 9.

Table 4 Summary of Simulated PK exposure Metrics for cUTI population (originally proposed CAZ/AVI doses in the label based on renal function)

Renal Function & Treatment	PK Parameter	Mean	SD	Median	Geom. Mean	Geom. CV	Min	Max
1. Normal 2000 mg CAZ+500 mg AVI q8h	AVI Cmax	13.0	2.65	12.8	12.7	62.0	5.01	24.0
	AVI Total Daily AUCss	127	29.8	124	124	62.3	57.0	297
	CAZ Cmax	70.7	19.4	68.1	68.2	63.0	21.3	161
	CAZ Total Daily AUCss	816	244	779	782	63.3	280	2260
2. Mild 2000 mg CAZ+500 mg AVI q8h	AVI Cmax	15.9	3.43	15.6	15.6	62.1	6.95	30.3
	AVI Total Daily AUCss	184	50.9	177	177	62.9	68.9	472
	CAZ Cmax	91.4	25.5	88.4	88.0	63.0	29.4	227
	CAZ Total Daily AUCss	1280	400	1210	1220	63.6	390	3840
3. Moderate 1000 mg CAZ+250 mg AVI q12h	AVI Cmax	9.77	2.15	9.63	9.54	62.2	3.67	19.0
	AVI Total Daily AUCss	112	31.9	108	108	63.0	44.7	277
	CAZ Cmax	51.1	14.2	49.1	49.1	63.0	16.4	123
	CAZ Total Daily AUCss	690	219	654	658	63.6	238	2070
4. Severe 1 1000 mg CAZ+250 mg AVI q24h	AVI Cmax	10.9	2.68	10.7	10.6	62.5	4.10	22.6
	AVI Total Daily AUCss	116	37.4	109	110	63.7	42.8	330
	CAZ Cmax	51.8	15.0	49.7	49.7	63.2	14.9	122
	CAZ Total Daily AUCss	615	210	581	582	64.0	195	2020
5. Severe 2 500 mg CAZ+125 mg AVI q24h	AVI Cmax	9.67	2.96	9.14	9.25	63.4	3.94	27.0
	AVI Total Daily AUCss	163	66.7	148	151	65.5	51.7	548
	CAZ Cmax	41.6	13.8	39.4	39.4	63.9	14.1	133
	CAZ Total Daily AUCss	700	277	645	651	65.2	209	2500
6. ESRD 500 mg CAZ+125 mg AVI q48h	AVI Cmax	7.54	1.53	7.39	7.39	61.9	2.98	13.9
	AVI Total Daily AUCss	106	23.5	103	103	62.1	46.0	238
	CAZ Cmax	70.4	35.2	60.8	63.4	67.0	16.1	381
	CAZ Total Daily AUCss	1380	811	1130	1200	69.4	286	8700

*For AVI and CAZ, Cmax is reported in mg/L and AUCss is reported in mg*h/mL.

Adopted from sponsor's population pharmacokinetics report, Appendix 16.1 .

Table 5 Median (Geometric CV as %) Predicted Ceftazidime Exposures in Simulated Patients with cIAI, Various Levels of Renal Function, and Different CAZ/AVI Doses.

Renal Function Group (CrCL range)	*Dose Regimen*	*$C_{max,ss}$ (µg/mL)*	*$AUC_{0-24,ss}$ (µg•h/mL)*	*%fT > MIC for an MIC of 8 mg/L*
Normal (> 80 mL/min)	2000 mg CAZ + 500 mg AVI, q8h[a]	45.5 (63)	518 (63)	83.9 (62)
	1000 mg CAZ + 250 mg AVI, q12h[b]	21.3 (63)	174 (63)	30.4 (10.3)[d]
	1000 mg CAZ + 250 mg AVI, q8h[c]	22.8 (63)	262 (63)	50.8 (17.1)[d]
	1500 mg CAZ + 375 mg AVI, q8h[c]	31.8 (63)	260 (63)	43.6 (63)
Mild (51-80 mL/min)	2000 mg CAZ + 500 mg AVI, q8h[a]	57.6 (63)	783 (64)	99.5 (61)
	1000 mg CAZ + 250 mg AVI, q12h[b]	25.5 (63)	265 (64)	49.6 (17.6)[d]
	1000 mg CAZ + 250 mg AVI, q8h[c]	29 (63)	396 (64)	86.7 (63)
	1500 mg CAZ + 375 mg AVI, q8h[c]	38 (63)	396 (64)	68.4 (63)

Abbreviations: $AUC_{0-24,ss}$ = area under plasma concentration-time curve over 24 hours at steady state; AVI = avibactam; CAZ = ceftazidime; $C_{max,ss}$ = maximum plasma drug concentration at steady-state; CrCL = creatinine clearance; ESRD = end-stage renal disease; %*f*T > MIC = % time that free drug concentrations are above the MIC over a dose interval; q8h = every 8 h; q12h = every 12 h; q24h = every 24 h; q48h = every 48 h.

a Proposed dose regimen

b Dose adjustment for moderate impairment in the NDA

c 50% increase in total daily dose compared to dose adjustment for moderate impairment in NDA

d Standard deviation is presented because the minimum is zero

Adopted from sponsor's response to information request, Table 8.3.

Table 6 Median (Geometric CV as %) Predicted Avibactam Exposures in Simulated Patients with cIAI, Various Levels of Renal Function, and Different CAZ/AVI Doses

Renal Function Group (CrCL range)	*Dose Regimen*	*$C_{max,SS}$ (mg/L)*	*$AUC_{0-24,SS}$ (mg•h/L)*	*%fT > C_T of 1 mg/L*
Normal (> 80 mL/min)	2000 mg CAZ + 500 mg AVI, q8h[a]	9.17 (62)	91.2 (62)	87.4 (62)
	1000 mg CAZ + 250 mg AVI, q12h[b]	4.41 (62)	30.5 (62)	39.8 (62)
	1000 mg CAZ + 250 mg AVI, q8h[c]	4.61 (62)	45.9 (62)	62.3 (63)
	1500 mg CAZ + 375 mg AVI, q8h[c]	6.61 (62)	45.7 (62)	49.8 (63)
Mild (51-80 mL/min)	2000 mg CAZ + 500 mg AVI, q8h[a]	11.0 (62)	126 (63)	99.5 (61)
	1000 mg CAZ + 250 mg AVI, q12h[b]	5.09 (62)	42.3 (63)	54.8 (63)
	1000 mg CAZ + 250 mg AVI, q8h[c]	5.52 (62)	63.2 (63)	88.7 (62)
	1500 mg CAZ + 375 mg AVI, q8h[c]	7.62 (62)	63.4 (63)	68.4 (63)

Abbreviations: $AUC_{0-24,ss}$ = area under plasma concentration-time curve over 24 hours at steady state; AVI = avibactam; $C_{max,ss}$ = maximum plasma drug concentration at steady-state; CAZ = ceftazidime; CrCL= creatinine clearance; ESRD = end-stage renal disease; %*f*T > C_T = % time that free drug concentrations are above a threshold concentration (C_T) over a dose interval; q8h = every 8 h; q12h = every 12 h; q24h = every 24 h; q48h = every 48 h.

a Proposed dose regimen

b Dose adjustment for moderate impairment in the NDA

c 50% increase in total daily dose compared to dose adjustment for moderate impairment in NDA

Adopted from sponsor's response to information request, Table 8.2.

3.3.2 Simulation of joint target attainment for dose regimens of interest

The CAZ and AVI population PK models were used to assess joint target attainment across six categories of renal function from normal to ESRD. %*f*T during which a patient's free drug concentration remained above the MIC for CAZ or above a desired threshold concentration for AVI was summarized for each renal function category to assess joint attainment for four potential target thresholds T1 through T4.

As shown in Table 1 at MICs of 1, 2, and 4 mg/L, all renal function categories achieved almost 100% joint target attainment for each of the four potential targets. The simulation results supported a PK/PD breakpoint of 8 mg/L, as PTA showed a distinct decrease between CAZ-AVI MIC values of 8 and 16 mg/L. At an MIC of 8 mg/L, the simulation results for a 120-minute IV infusion with the dose adjustments based on renal function showed that all renal function categories achieve over 90% PTA of the strictest joint target (50% *f*T>MIC for ceftazidime and 50% *f*T>1.0 mg/L for avibactam), except "Severe 1", where joint target attainment was 86%. Results for the cUTI population (Table 2) were reasonably consistent with the cIAI simulations, with overall higher joint target attainment due to the population-associated increases in typical exposures.

3.4 Sponsor's conclusion

CAZ PK following IV dose administration was well described by a two-compartment model with first-order elimination The primary predictors of variability in CAZ PK were disease status (with decreased exposure for both cIAI and cUTI patients versus HV), CrCL, race (Japanese versus non-Japanese), and body weight.

AVI PK following IV dose administration was well described by a two-compartment model with first-order elimination. The primary predictors of variability in AVI PK were disease status (with decreased exposure for both cIAI and cUTI patients versus HV), renal function category (i.e., ESRD and ARC), CrCL, and body weight.

Exposure-response analyses of individual exposures and microbiologic outcomes in Phase II cIAI and cUTI patients revealed that almost all CAZ %*f*T >MIC and AVI %*f*T >0.5 mg/L values were close to 100% and unfavorable microbiologic outcomes (i.e., treatment failure) were relatively infrequent; thus, formal exposure-response modeling was not feasible. While a reduction in AVI %*f*T>1.0 mg/L in subjects with unfavorable microbiologic response was observed, the reduction was not statistically significant.

In simulations based on the final CAZ and AVI PK models, at MICs of less than 8 mg/L, all renal function categories achieved almost 100% joint target attainment for the potential targets T1 through T4. At an MIC of 8 mg/L, the "Severe 1" group achieved greater than 90% joint target attainment for T1 and T3, and 85-86% target attainment for T2 and T4.

Overall, the simulation results support a PK/PD breakpoint of 8 mg/L across renal function groups with the dose adjustments described. Adequate PTAs are predicted for the dose regimens in ongoing Phase 3

trials (subjects with normal renal function, mild, moderate and “Severe 1” renal impairment) and for the proposed dose regimens for subjects with “Severe 2” renal function and ESRD.

Reviewer’s comment: An exposure-response relationship cannot be identified due to the limited number of subjects and low number of unfavorable outcomes in Phase II studies. Instead, the developed population PK models and selected CAZ/AVI targets (percent of time where free concentration exceeded an MIC value) was used to assess joint target attainment across renal function groups with dose adjustment to determine the PK/PD breakpoint. The proposed breakpoint based on population PK model is acceptable based on the Applicant’s simulations and clinical data from the Phase II studies.

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/s/

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01/20/2015

KIMBERLY L BERGMAN
01/20/2015