BRIEFING PACKAGE

Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

NDA 206494

CEFTAZIDIME-AVIBACTAM

APPLICANT: CEREXA, INC

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

DECEMBER 5, 2014

PROPOSED INDICATIONS:

COMPLICATED INTRA-ABDOMINAL INFECTIONS (CIAI),
COMPLICATED URINARY TRACT INFECTIONS (CUTI), INCLUDING ACUTE PYELONEPHRITIS (AP), AND
AEROBIC GRAM-NEGATIVE INFECTIONS WITH LIMITED TREATMENT OPTIONS

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Table of Contents

1. INTRODUCTION

Ceftazidime-avibactam (CAZ-AVI) is a combination of ceftazidime, a third-generation cephalosporin antibacterial drug, and avibactam (formerly NXL104, AVE1330), a non-β-lactam, β-lactamase inhibitor (BLI). The avibactam component is a new chemical entity that is not currently marketed in any country, either alone or in combination. Avibactam protects ceftazidime from degradation by β-lactamase enzymes and maintains the antibacterial activity of ceftazidime against isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* that express several types of serine β-lactamases. Avibactam alone has no direct antibacterial activity (at concentrations achieved in humans at the proposed dose) and does not affect the activity of ceftazidime against ceftazidime-susceptible (CAZ-S) organisms or most anaerobic gram-negative rods.

The Applicant has submitted a new drug application (NDA) for CAZ-AVI through the 505(b)(2) pathway, relying on the Agency's previous findings of efficacy and safety of ceftazidime, as well as published literature on ceftazidime. Nonclinical and Phase 1 clinical data in the NDA include pharmacology/toxicology studies, microbiological surveillance, data from animal models of infection, clinical pharmacology studies with avibactam (alone and in combination), and pharmacokinetic/pharmacodynamics (PK/PD) target attainment analyses. Descriptive efficacy and safety data from two Phase 2 studies, one each in complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including subsets of subjects with CAZ-nonsusceptible (CAZ-NS) pathogens and preliminary experience from an open-label trial for patients with infections due to CAZ-NS pathogens are submitted in the NDA. A Phase 3 trial in hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) is ongoing. Phase 3 trials in cUTI and cIAI were recently completed.

The Applicant is seeking the following indications for CAZ-AVI:

- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (cUTI), including acute pyelonephritis (AP)
- Aerobic gram-negative infections with limited or no alternative treatment options including HABP/VABP

2. BACKGROUND

2.1. REGULATORY HISTORY

Ceftazidime was approved in 1985 under the trade name FORTAZ®. The currently labeled indications as described in the US package insert[1] are summarized in Table 1.

Table 1: Currently Labeled Indications for Ceftazidime

Indication	Pathogens
Lower respiratory tract infections	*P. aeruginosa*, *H. influenzae*, *Klebsiella* spp, *Enterobacter* spp, *P. mirabilis*, *Pseudomonas* spp, *E. coli*, *Serratia* spp, *Citrobacter* spp, *S. pneumoniae*, *S. aureus* (methicillin-susceptible strains)
Skin and skin structure infections	*P. aeruginosa*, *Klebsiella* spp, *E. coli*, *Enterobacter* spp, *Proteus* spp including *P. mirabilis* and indole+ *Proteus*, *Serratia* spp, *S. aureus* (methicillin-susceptible strains), *S. pyogenes* (group A beta hemolytic streptococci)
Urinary tract infections	*P. aeruginosa*, *Enterobacter* spp, *Proteus* spp including *P. mirabilis* and indole+ *Proteus*, *Klebsiella* spp, and *E. coli*
Bacterial septicemia	*P. aeruginosa, Klebsiella* spp, *H. influenzae, E. coli*, *Serratia* spp, *S. pneumoniae*, *S. aureus* (methicillin-susceptible)
Gynecological infections	*E. coli*
Intra-abdominal infections	*E. coli*, *Klebsiella* spp, *S. aureus* (methicillin-susceptible) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *B. fragilis* are resistant)
Central nervous system infections	*H. influenzae*, *N. meningitidis,* and limited: *P. aeruginosa, S. pneumoniae*

Increasing resistance to cephalosporins, particularly in the hospital setting, has resulted in more widespread use of the carbapenems due to their inherent stability to extended spectrum β-lactamase (ESBL) and AmpC β-lactamases.[2,3] Although other β-lactam-β-lactamase inhibitor (BL-BLI) combinations have been approved, the activity of these combinations do not include Ambler Class A *Klebsiella pneumoniae* carbapenemases (KPCs), Class B enzymes (metallo-β lactamases, e.g. NDM-1), Class C enzymes (e.g. AmpC) and may induce ESBL production. Avibactam inhibits Class A ESBLs, KPCs, AmpC, and some Class D enzymes, but is not active against the metallo-β lactamases (Class B). The clinical development program for CAZ-AVI was designed to address this unmet need.

The initial Investigational New Drug (IND) application was submitted by Novexel in January 2008. Novexel transferred ownership to AstraZeneca in April 2010, who then transferred ownership to Cerexa, Inc., a wholly owned subsidiary of Forest Laboratories, Inc. in October 2011.

On 11 March 2013, the Agency designated CAZ-AVI as a qualified infectious disease product (QIDP) with Fast Track Designations for cIAI, cUTI and HABP/VABP. In December 2013, the Applicant and Agency agreed that an NDA package based upon nonclinical data, Phase 1 data, data from two Phase 2 studies, and published ceftazidime data could be submitted through the 505(b)(2) pathway. A summary of completed and ongoing clinical studies are summarized in Table 2 and Table 3, respectively.

Table 2: 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

Table 3: Ongoing and Recently Completed Clinical Studies

Study ID	Study Type/Population	Blinded
Phase 3 Clinical Efficacy and Safety Studies		
D4281C00001	HABP/VABP/Infected hospitalized adults	yes
D4280C00001/5[a]	cIAI/Infected hospitalized adults	yes
D4280C00002/4[b]	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 adults	no

[a] Subjects enrolled under identical study protocols D4280C00001 and D4280C00005 are combined into one study database (D4280C00001/5). Trial recently completed; data unblinded; preliminary results available.

[b] Subjects enrolled under identical study protocols D4280C00002 and D4280C00004 are combined into one study database (D4280C00002/4). Trial recently completed; results not available.

The Applicant's proposed indications for CAZ-AVI are:

- Complicated intra-abdominal infections (when used in combination with metronidazole) proven or suspected to be caused by the following gram-negative pathogens: *Escherichia coli*, *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.
- Complicated urinary tract infections (cUTI), including acute pyelonephritis (AP), proven or suspected to be caused by the following gram-negative pathogens: *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Enterobacter*

cloacae, *Citrobacter freundii*, *Proteus* spp. (including *Proteus mirabilis* and indole-positive *Proteus*), and *Pseudomonas aeruginosa*.

- Aerobic gram-negative infections with limited or no alternative treatment options including HABP/VABP and the infection is proven or suspected to be caused by the following 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*.

The proposed 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 for up to 14 days in patients ≥ 18 years of age. Patients with renal impairment should have the dosage of CAZ-AVI modified according to the estimated measured creatinine clearance (CrCl) (Table 4).

Table 4: **Dosage of CAZ-AVI in Patients with Renal Impairment**

Estimated Creatinine Clearance (mL/min)[a]	***Recommended Dosage Regimen for CAZ-AVI***
> 50	No dosage adjustment necessary
≥ 31 to ≤ 50	1.25 g (1 g ceftazidime + 0.25 g avibactam) IV (over 2 hours) every 12 hours
≥ 16 to ≤ 30	1.25 g (1 g ceftazidime + 0.25 g avibactam) IV (over 2 hours) every 24 hours
≥ 6 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, CAZ-AVI should be administered after hemodialysis on hemodialysis days.

2.2. 505(B)(2)

Section 505 of the Federal Food, Drug, and Cosmetic Act describes three types of new drug applications. One of these types, described in section 505(b)(2), is an NDA that contains full reports of investigations of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. This provision expressly permits the FDA to rely on the Agency's previous finding of safety and effectiveness for an approved drug.[4]

The Agency's regulatory approach to this NDA is to rely on the Agency's prior finding of safety and effectiveness of ceftazidime. The contribution of avibactam will be demonstrated by in vitro studies, animal models of infection and with limited clinical data. Safety of avibactam will be determined from Phase 1 studies of avibactam alone and phase 1 and 2 studies of CAZ-AVI.

Labeling resulting from such a program will include a limited use statement that the product only be used when other therapeutic options are not suitable.

2.3. FIXED DRUG COMBINATIONS

For fixed drug combinations, the Applicant must demonstrate the contribution of each component in a combination under the requirements of 21 CFR § 300.50. When the combination rule is applied to a BL-BLI combination product such as CAZ-AVI, confirmatory clinical trials comparing ceftazidime alone to CAZ-AVI may not be feasible. The contribution of both components can be demonstrated by in vitro studies and in animal models of infection, where the addition of avibactam restores the activity of ceftazidime against ceftazidime-nonsusceptible microorganisms. Limited clinical data from subgroups of patients with ceftazidime-nonsusceptible microorganisms can be described as well.

3. CLINICAL PHARMACOLOGY

Ten Phase 1 studies have been completed as part of the CAZ-AVI development program with avibactam alone or CAZ-AVI (Table 2). The basic pharmacokinetic (PK) properties of ceftazidime are cited from the approved drug label (Fortaz® US Prescribing Information[1]) and published literature. Ceftazidime PK data are available from seven of the Phase 1 CAZ-AVI studies and the two Phase 2 CAZ-AVI studies.

3.1. SUMMARY OF PHARMACOKINETICS

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 CAZ-AVI 2.5 g (2 g ceftazidime and 0.5 g avibactam) administered every 8 hours are summarized in Table 5. The PK of ceftazidime was approximately dose-proportional. Avibactam also demonstrated approximately linear PK across the dose range studied (50 mg to 2000 mg) for single IV administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple IV infusions of CAZ-AVI 2.5 g (2 g ceftazidime and 0.5 g avibactam) administered every 8 hours for up to 11 days in healthy adults with normal renal function.

Table 5: 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 CAZ-AVI 2.5 g [a] Dose Administered as a 2-hour Infusion (n = 16)**	**Multiple CAZ-AVI 2.5 g [a] Doses Administered q8h as 2-hour Infusions for 11 Days (n = 16)**	**Single CAZ-AVI 2.5 g [a] Dose Administered as a 2-hour Infusion (n = 16)**	**Multiple CAZ-AVI 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]: $AUC_{0\text{-}inf}$ reported for single dose administration; $AUC_{0\text{-}tau}$ reported for multiple dose administration.[c]: n = 15. [d]: n = 13.

Distribution

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 steady-state volumes of distribution of ceftazidime and avibactam were 17.0 L and 22.2 L, respectively, in healthy adults following multiple doses of CAZ-AVI 2.5 g infused every 8 hours over 2 hours for 11 days.

Metabolism

Ceftazidime is mostly eliminated as unchanged drug (80% to 90% of the dose). No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes).

Excretion

Both ceftazidime and avibactam are eliminated primarily by the kidneys.

Approximately 80% to 90% of an IV dose of ceftazidime is excreted unchanged by the kidneys over a 24-hour period. The mean renal clearance of ceftazidime was approximately 100 mL/min. The calculated plasma clearance of approximately 115 mL/min indicated nearly complete elimination of ceftazidime by the renal route.

Following administration of a single 0.5 g IV dose of radiolabelled avibactam, an average of 85% of administered avibactam was recovered from the urine as unchanged drug within 96 hours. Renal clearance was 158 mL/min suggesting active tubular secretion of avibactam.

Other key PK findings for CAZ-AVI

- Dose adjustments based on age (young adult or elderly) or gender are not required.
- There is no drug -drug interaction (DDI) between ceftazidime and avibactam. Ceftazidime did not alter the exposure of avibactam as measured by AUC and C_{max} following a single dose or 3 days of multiple-dose administration q8h. Avibactam did not alter the exposure of ceftazidime following a single dose or 3 days of multiple-dose administration q8h.
- There is no DDI between CAZ-AVI and metronidazole. Metronidazole had no effect on the systemic exposure of ceftazidime or avibactam when it was administered immediately before CAZ-AVI as a single dose or q8h for 3 days compared to when CAZ-AVI was administered alone. CAZ-AVI had no effect on the systemic exposure of metronidazole when it was administered immediately after metronidazole as a single dose or q8h for 3 days compared to when metronidazole was administered alone.
- Avibactam is a substrate of OAT1 and OAT3 in vitro. In vitro uptake of avibactam by OAT1 and OAT3 was not inhibited by ceftazidime but was inhibited by probenecid.
- Following administration of CAZ-AVI 2.5 g (2 g ceftazidime + 0.5 g avibactam) to healthy male subjects q8h as a 2-hour infusion for 3 days, the C_{max} and $AUC_{0-\tau}$ values of

avibactam in extracellular lung fluid (ELF) were 28% to 35% and 32% to 35% of the plasma C_{max} and $AUC_{0-\tau}$, respectively. The C_{max} and $AUC_{0-\tau}$ values of ceftazidime in ELF were approximately 23% to 26% and 31% to 32% of the plasma C_{max} and $AUC_{0-\tau}$, respectively. Note that these values are similar to or higher than those observed in mice.

- No dose adjustment is needed for CAZ-AVI in patients with hepatic impairment.
- Avibactam exposure was found to increase with increasing severity of renal impairment such that dosage adjustments are required in patients with moderate (31 mL/min ≤ CrCl ≤ 50 mL/min) or severe (6 mL/min ≤ CrCl ≤ 30 mL/min) renal impairment and end-stage renal disease (ESRD, CrCl ≤ 5 mL/min) (Table 6).

Table 6: Avibactam PK Parameters (Geometric Mean [CV%]) Following a Single 30-minute IV Infusion of 100 mg Avibactam in Subjects with Varying Degrees of Renal Impairment

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]	—	1.2	1.2	1.4	1.4
$T_{½}$, 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]	—	2.6	3.8	7.0	19.5
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]	—	0.381	0.261	0.142	0.051

[a]: Ratio of geometric means (reference = normal renal function). ESRD: End-stage renal disease; NS: Not statistically significant (p > 0.2)

3.2. Target Attainment Analysis for Efficacy

Determination of PK/PD target

The percent time of free-drug concentrations that are above the minimum inhibitory concentration (MIC) over a dose interval (% *f*T > 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 (% *f*T > 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% *f*T > MIC for infections due to *Staphylococcus aureus, Streptococcus pneumoniae,* and *Enterobacteriaceae*.

The C_T for AVI has been estimated as 0.5 mg/L in hollow fiber model experiments with cephalosporins, using three ceftazidime-resistant strains of *Enterobacteriaceae*: *E. cloacae* 293HT96 (derepressed Class C AmpC: MIC of ceftazidime >128 mg/L; MIC of CAZ-AVI = 4 mg/L); *K. pneumoniae* 283CF5 (Class A SHV-5: MIC of ceftazidime = 64 mg/L; MIC of CAZ-AVI = 2 mg/L); and *K. pneumoniae* Tunisie K4 (Class A CTX-M-15 & TEM-1, class D OXA-1: MIC of ceftazidime ≥128 mg/L; MIC of CAZ-AVI = 1 mg/L). Studies of *Enterobacteriaceae* in the hollow-fiber system showed that in the background of simulated human PK 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.

The PK/PD target of avibactam was also 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 %*f*T > 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 %*f*T > 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 *f*T > 1 mg/L of 45.0-48.4%.

The mean magnitude of avibactam %*f*T > 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% *f*T > 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*.

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)

The population PK models for ceftazidime and avibactam were used to conduct a PK/PD target attainment analysis to support CAZ-AVI dose selection for subjects with different levels of renal function, as follows (Study CAZ-MS-04):

- CrCl > 80 mL/min (representing normal renal function [NORM])
- 51 mL/min ≤ CrCl ≤ 80 mL/min (representing mild renal impairment [MILD])
- 31 mL/min ≤ CrCl ≤ 50 mL/min (representing moderate renal impairment [MOD])
- 16 mL/min ≤ CrCl ≤ 30 mL/min (representing severe renal impairment at the upper portion of the CrCl interval [SEV1])
- 6 mL/min ≤ CrCl ≤ 15 mL/min (representing severe renal impairment at the lower portion of the CrCl interval [SEV2])
- 0 mL/min < CrCl ≤ 5 mL/min (representing ESRD)

Demographic covariates and CrCl for 5000 subjects were simulated for each renal function group. Because cIAI subjects showed lower exposures than healthy volunteers (Study CAZ-MS-01) and cUTI subjects (Study CAZ-MS-03), the cIAI population was used to simulate exposures and calculate associated target attainment. Because the ceftazidime population PK model dataset did not contain any ceftazidime concentration data in subjects with moderate or worse renal impairment, data from the literature were used to derive the relationship between clearance and CrCl for subjects with CrCl < 50 mL/min.

The PTA 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 PTA). 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 nonclinical microbiological data (i.e., hollow fiber infection models and animal models of infection) were used. The joint PK/PD target used for PTA analysis was 50 %*f*T > MIC for ceftazidime and 50 %*f*T > 1.0 mg/L for avibactam. The results for a 2-hour IV infusion are shown below in Table 7, with target attainment by renal function group at the proposed dose regimen.

Table 7: 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

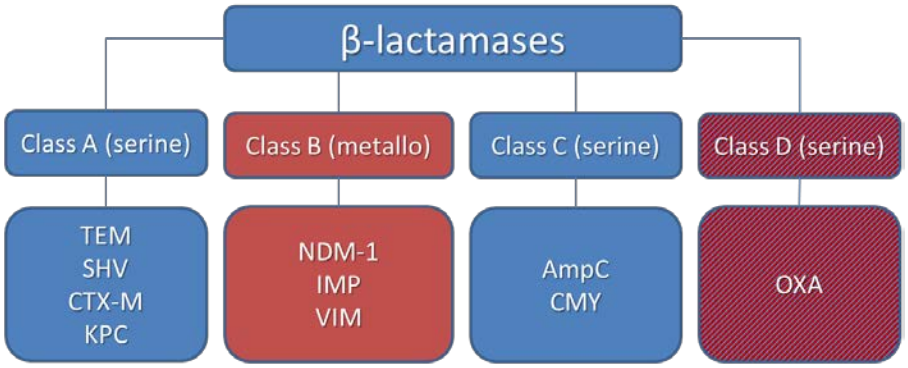
Renal function	*Proposed Dose regimen*	*% of simulated patients achieving PK/PD target*
CAZ-AVI MIC=4 µg/mL		
NORM	2000 mg CAZ + 500 mg AVI, q8h	98.9
MILD	2000 mg CAZ + 500 mg AVI, q8h	99.9
MOD	1000 mg CAZ + 250 mg AVI, q12h	98.9
SEV1	1000 mg CAZ + 250 mg AVI, q24h	97.8
SEV2	500 mg CAZ + 125 mg AVI, 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

4. MICROBIOLOGY

4.1. ANTIBACTERIAL SPECTRUM OF ACTIVITY

Ceftazidime in combination with avibactam extends the in vitro and in vivo activity of ceftazidime against clinically important gram-negative bacteria including *P. aeruginosa* and bacteria belonging to the family *Enterobacteriaceae*. When used in combination, avibactam protects ceftazidime from degradation by serine β-lactamase enzymes and maintains the antibacterial activity of ceftazidime against isolates associated with multidrug resistance. CAZ-AVI is capable of overcoming some AmpC-mediated resistance in *P. aeruginosa,* and against *Enterobacteriaceae* CAZ-AVI demonstrates activity against Class A, C and some Class D ESBL producing isolates (Figure 1).

Figure 1: Classes of β-lactamases and BLI Activity



The activity of CAZ-AVI was assessed against *Enterobacteriaceae* and *P. aeruginosa* isolates associated with cIAI and cUTI. Table 8 shows 2012 microbiological surveillance data with gram-negative bacterial isolates collected from 73 US medical centers from patients with cUTI. Table 9 shows 2012 microbiological surveillance data with gram-negative bacterial isolates collected from 73 US medical centers from patients with cIAI. CAZ-AVI was active against a collection of ceftazidime non-susceptible *Enterobacteriaceae* and some meropenem non-susceptible *P. aeruginosa*.

Table 8: Activity of CAZ-AVI against cUTI Pathogens Collected in the US in 2012

Organisms	Phenotype	cUTI	
		MIC_{90} (mg/L)	
		CAZ-AVI	Ceftazidime
E. coli	All (913)	0.12	0.5
	ESBLs (78)	0.25	32
	Non-ESBLs (835)	0.12	0.25
Klebsiella spp.	All (501)	0.25	8
	ESBLs (65)	1	>32
	Non-ESBLs (436)	0.25	0.5
	Meropenem-S (501	0.25	8
Enterobacter spp.	All (183)	0.5	>32
	CAZ-S (145)	0.25	0.5
	CAZ-NS (38)	1	>32
Citrobacter spp.	All (110)	0.25	16
Proteus spp.	All (181)	0.12	4
Providencia spp.	All (111)	0.25	1
Serratia spp.	All (45)	0.5	1
P. aeruginosa	All (82)	4	16
	Meropenem-S (69)	4	8
	Meropenem-R (13)	8	>32

Table 9: Activity of CAZ-AVI against cIAI Pathogens Collected in the US in 2012

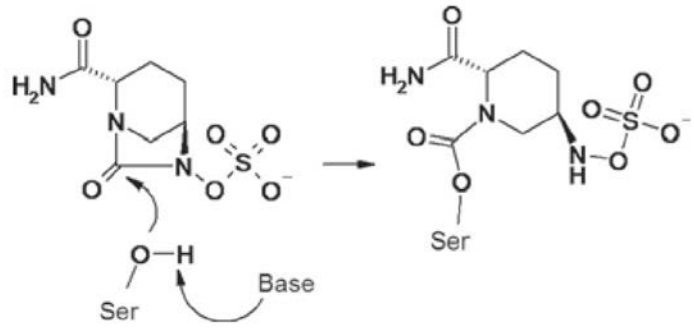
Organisms	Phenotype	cUTI	
		MIC_{90} (mg/L)	
		CAZ-AVI	Ceftazidime
E. coli	All (162)	0.12	1
	ESBLs (17)	0.5	>32
	Non-ESBLs (147)	0.12	0.25
Klebsiella spp.	All (103)	0.5	32
	ESBLs (17)	2	>32
	Non-ESBLs (87)	0.25	0.5
	Meropenem-S (97)	0.25	1
	Meropenem-NS (7)	0.12-2	16->32
Enterobacter spp.	All (69)	0.5	>32
	CAZ-S (45)	0.5	1
	CAZ-NS (24)	1	>32
Citrobacter spp.	All (25)	0.5	>32
Proteus spp.	All (25)	0.06	0.12
Providencia spp.	All (10)	0.25	0.25
Serratia spp.	All (11)	0.5	0.5
P. aeruginosa	All (82)	4	32
	Meropenem-S (69)	4	8
	Meropenem-R (13)	8	>32

4.2. MECHANISM OF ACTION

Ceftazidime is a semisynthetic, third-generation cephalosporin, β-lactam antibacterial drug that exerts its primary effect by inhibition of enzymes responsible for cell wall synthesis. Ceftazidime shows high affinity for penicillin binding protein (PBP) 3 of *P. aeruginosa* and *E. coli*, with IC_{50} values of 0.06-0.22 mg/L in competitive binding experiments. Ceftazidime also competes for binding to PBPs 1a and 1b, but with 2- to 84-fold lower affinity. Gram-negative bacteria form filaments when exposed to ceftazidime at concentrations similar to the IC_{50} for PBP3; however, upon exposure to higher concentrations, cell lysis occurs.

Avibactam is a diazabicyclooctanone, non-β-lactam, β-lactamase inhibitor. Avibactam inhibits class A ESBLs and carbapenemases, class C β-lactamases and some class D oxacillinases and carbapenemases. It is hypothesized that the inhibition of β-lactamases by avibactam occurs when the inhibitor binds to the catalytic serine residue in the active site of the enzyme, giving rise to a highly stable carbamoyl linkage (Figure 2).

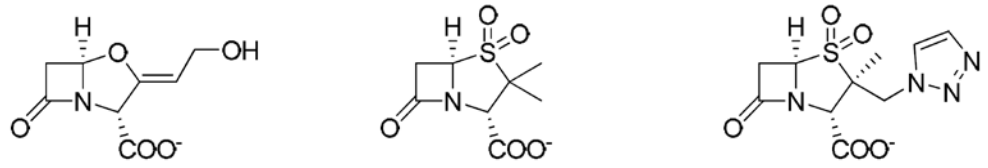
Figure 2: Proposed Molecular Mechanism of Action of Avibactam



Source: Stachyra et al 2010.[5]

Avibactam differs from other β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam (Figure 3) in three key aspects.

Figure 3: Chemical Structures of Clavulanic Acid, Sulbactam, and Tazobactam



Structurally, avibactam is a [3,2,1]-diazabicyclooctanone derivative that employs a reactive urea rather than a β-lactam to inhibit serine β-lactamases. Second, the mechanism of avibactam inhibition of β-lactamases is covalent, but reversible, in contrast to clavulanic acid, sulbactam and tazobactam which are also covalent but irreversible. Third, avibactam has an expanded spectrum of β-lactamase inhibition compared to the other three molecules, which are largely limited to coverage of class A enzymes. Avibactam inhibits class A ESBLs, class A

carbapenemases such as KPC-2, some class C enzymes of the AmpC family, and some class D OXA enzymes. Table 10 shows the biochemical inhibition (IC_{50}) of class A, C and D β-lactamases.

Table 10: Biochemical Inhibition (IC_{50}) of Class A, C and D β-lactamases by Avibactam

Enzyme and class	*IC_{50} (nM)*			
	Avibactam	*Clavulanic acid*	*Tazobactam*	*Sulbactam*
Class A				
TEM-1	8	58, 130	32	1560
CTX-M-15	5	12	6	230
KPC-2	170	> 100000	50000	57000
KPC-3 [a]	28	4900	ND [b]	ND
SHV-4	3	4	55	260
Class C				
P99	100	> 100000	1300	21100
P. aeruginosa AmpC	128	> 100000	4600	27000
Class D				
OXA-40 a	5100	9200	ND	ND

a These enzymes were tested with a 40 min pre-incubation.

b ND = not determined

Source: Bonnefoy et al 2004[6], Stachyra et al 2010[5], Study CAZ104-M2-018-NXL104-BI0001

4.3. Mechanism of Resistance

Resistance to cephalosporins may be mediated through a variety of mechanisms including the alterations of PBPs, formation of cephalosporinases that inactivate the drug, a decrease in the ability of the drug to penetrate the cell wall and reach the drug target, or efflux of the drug thereby preventing the drug from reaching its target. In gram-negative organisms, the predominant mode of resistance is the production of β-lactamase hydrolyzing enzyme. In avibactam mutant selection studies, frequencies for stable mutants from *P. aeruginosa* and Enterobacteriaceae with ESBL, AmpC or KPC β-lactamases were assessed and ranged from 2.04×10^{-9} to 1.8×10^{-6}. Stable *E. coli* mutants had a CTX-M-15 sequence change (Lys237Gln). Resistance to avibactam in *Enterobacter cloacae* was determined to be associated with amino acid deletion in AmpC, loss of OmpC and/or OmpF.

4.4. Animal Models of Infection

CAZ-AVI was studied in five animal models of infections caused by Class A and Class C serine β-*lactamase*-producing bacteria.

Murine Systemic Infection

In this model, separate experimental systemic infections induced by seven *Enterobacteriaceae* isolates were established by intraperitoneal injection to obtain an inoculum between 10-100 times the lethal dose. Mice were treated subcutaneously at 0 and 4 hours post infection with CAZ-AVI (4/1 w/w) and comparators (cefepime, piperacillin-tazobactam (8/l-w/w), co-amoxiclav

(4/1 w/w). The activity of ceftazidime was restored when combined with avibactam against all seven isolates. This was demonstrated by a survival advantage with CAZ-AVI (ED_{50} range: 5 - 29 mg/kg for class A producers and ED_{50} range: < 5 - < 15 mg/kg for class C producers) compared to ceftazdime alone (ED_{50} > 50 mg/kg). Cefepime was active against six out of the seven isolates at levels similar to CAZ/AVI. Piperacillin-tazobactam and co-amoxiclav were generally less effective than CAZ-AVI against class A producing strains and totally inactive against all AmpC producers.

Pneumonia Immune-Compromised Mice

CAZ-AVI (4/1 w/w) was compared to ceftazidime alone, ceftazidime-clavulanate (4/1 and 2/1-w/w), and imipenem, in a mouse model of pneumonia induced by *K. pneumoniae.* Pneumonia was induced by intranasal inoculation of mice with about 4 x 10^6 CFU of *K. pneumoniae* 283KB4 (AmpC DHA-2) or *K. pneumoniae* 283KB5 (AmpC LAT-4 + SHY-11). Mice were treated three times a day for two days, beginning 16-18 h after infection. Untreated animals developed bacteremic pneumonia and fatal disease within two to four days; the bacterial lung load 16-18 hours post infection was around 10^{11} CFU/g of lung tissue. Ceftazidime alone showed no activity. CAZ-AVI demonstrated a significant 5-6 $\log_{10}$ reduction in lung bacterial counts 48h after therapy initiation. Imipenem showed similar efficacy to CAZ-AVI.

Pyelonephritis Immune-Compromised Mice

CAZ-AVI was compared to ceftazidime alone, ceftazidime-clavulanate (4/1 -w/w), and imipenem, in a mouse model of pyelonephritis induced by ceftazidime-resistant *K. pneumoniae* (Class A + AmpC), *E. coli* (one Class A and one AmpC), *E. cloacae* (AmpC), *M. morganii* (AmpC), or *C. freundii* (AmpC). Pyelonephritis was induced by direct inoculation in the kidney with about 10^4 CFU of each bacterial strain. Mice were treated four times, at 4, 8, 24 and 32 hour after infection, with ceftazidime or imipenem alone at 10 or 25 mg/kg, or with ceftazidime-clavulanate or CAZ-AVI. The in vivo efficacy was monitored using bacterial kidney clearance; in untreated animals, the bacterial load 48 hours post-infection was between the ranges of 10^5 - 10^7 CFU/kidney. Ceftazidime alone was ineffective against all six strains compared to the non-treated control group. In each case, the CAZ-AVI demonstrated efficacy with a significant 2.6-4.5 $\log_{10}$ reduction in kidney bacterial counts 48h after therapy initiation. Overall, imipenem showed similar efficacy to CAZ-AVI, while the ceftazidime-clavulanate combination was active against one isolate.

Meningitis Immune-Competent Rabbits

CAZ-AVI was also evaluated in rabbits infected with 10^5 CFU of *K. pneumoniae* 283KB4 (AmpC DHA-2) by direct injection into the subarachnoid space. About 18 hours following the infection, the animals were treated at T_0 with intravenous injections of the CAZ/AVI (ceftazidime 150 mg/kg; ratio 4/1) or meropenem (125 mg/kg). The animals received a second injection of ceftazidime alone (150 mg/kg) or meropenem (125 mg/kg) alone, four hours later. Cerebrospinal fluid and blood were sampled from T_0 to 8 hours following initiation of antibacterial therapy and tested for CAZ-AVI and meropenem concentrations; in addition, bacterial titers were measured in cerebrospinal fluid. Bacterial titers in cerebrospinal fluid were significantly decreased following treatment with CAZ-AVI combination: > 5 log reduction at 8

hours after initiation of therapy. Meropenem decreased bacterial load to a lower extent than CAZ-AVI (statistical significance at $p < 0.05$). Ceftazidime alone was without clinically significant effect (0.10 $\log_{10}$ reduction in bacterial load, as compared with 0.47 $\log_{10}$ increase for untreated rabbits).

Murine Thigh infection

The efficacy of CAZ-AVI was evaluated in a mouse neutropenic thigh infection model against *K. pneumoniae* (KPC; MIC ≥256 mg/L) and *P. aeruginosa*. For *K. pneumoniae,* thigh infection was induced by the intramuscular injection of the KPC-producing isolate into the right thigh. Mice were treated 1.5 hour post-infection with either CAZ alone or CAZ-AVI (4:1 w/w). After thighs were removed at 24 hours post-infection, a >2-$\log_{10}$ CFU reduction was observed for mice treated with CAZ-AVI (4:1 w/w) at doses of equal to 128:32 mg/kg compared to CAZ doses of equal to 1,024 mg/kg which were unable to reduce the numbers of CFUs. For *P. aeruginosa,* thigh infection was induced by an inoculum of 10^8 CFU in non-neutropenic mice and 10^7 CFU in neutropenic animals. Human simulated CAZ-AVI therapy commenced 2 hours after infection. Human simulated dosage resulted in bacterial reductions of 0.3 to 1.95 $\log_{10}$ CFU, and 13 of 15 achieved a reduction of ≥ 0.75 $\log_{10}$ CFU in non-neutropenic mice which also included three animals that had CAZ-AVI MICs of ≤16 mg/L. In the neutropenic study, CAZ-AVI treatment resulted in bacterial load reductions based on CAZ-AVI MIC; bacterial killing was observed for 16 of 17 isolates with CAZ-AVI MIC of ≤8mg/L and five of eight isolates with CAZ-AVI MICs of ≤16 mg/L.

In summary, CAZ-AVI demonstrated bacterial clearance from the lung in mouse pneumonia models, from the cerebrospinal fluid in a rabbit meningitis model, and from the kidney in a mouse pyelonephritis model. In a mouse systemic infection model, CAZ-AVI was associated with improved survival compared with ceftazidime alone. The combination of ceftazidime-avibactam demonstrates efficacy against *P. aeruginosa* and a range of *Enterobacteriaceae* isolates in animal infection models where ceftazidime alone was ineffective (Table 11).

Table 11: Overview of Animal Models of Infection

Disease Model and Animal	Pathogens	Results
Systemic infection Immune-competent mice	Class A and Class C *Enterobacteriaceae*	Survival with CAZ: ED_{50} > 50 mg/kg CAZ-AVI: ED_{50} 5 to 29 mg/kg
Pneumonia Immune-compromised mice	48 hr post infection 10^{11} CFU/g of lung tissue *K. pneumoniae* (ESBL)	bacterial clearance* in the lung (↓5-6 $\log_{10}$), untreated animals developed bacteremic pneumonia died within 2-4 days
Pyelonephritis Immune-compromised mice	48 hr post infection 10^5 to 10^7 CFU/kidney (ESBL/AmpC) *K. pneumo, E. coli*, *E. cloacae*, *M. morganii*, *C. freundii*	bacterial clearance* in kidney (↓2.6 to 4.5 $\log_{10}$)
Meningitis Immune-competent Rabbit	*K. pneumoniae* (AmpC)	bacterial clearance* in CSF >5 $\log_{10}$ reduction at 8 h
Murine Thigh infection	*K. pneumoniae* (KPC) *P. aeruginosa*	*K. pneumoniae*:↓bacterial load by >2 $\log_{10}$ *P. aeruginosa*: ↓load by ≤1.95 $\log_{10}$ (non neutropenic and ≤ 3.4 $\log_{10}$ (neutropenic)

* For CAZ-AVI. There was no reduction in bacterial load in animals treated with CAZ alone.

5. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

Following IV administration of avibactam to rats and dogs, exposure increased in approximate proportion to dose. There was no evidence of accumulation in either species after multiple doses and exposure in males and females was comparable. The steady state volume of distribution ranged from 0.61 to 0.66 L/kg in rats and from 0.26 to 0.67 L/kg in individual dogs. Protein binding of avibactam was low at < 22.1% bound across human, mouse, dog, rabbit, and rat. Binding was found to be concentration-dependent in animal plasma, but not in human plasma (0.25 to 2500 mg/L). Avibactam is approximately 8.2% bound in human plasma. In a quantitative tissue distribution study in rats, three tissues/organs exhibited an exposure to radioactivity related to administered [^{14}C]-avibactam greater than plasma: kidneys, bladder, and whole blood. All other tissues and organs showed lower avibactam related exposure than plasma. In separate tissue distribution studies, avibactam was also detected in CSF and lung epithelial lining fluid (ELF) of mice at exposures lower than plasma. No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes) and hence, no enzyme responsible for metabolism (if any) could be identified. Avibactam showed no significant inhibition of CYP enzymes, and no in vitro CYP induction potential within the clinically relevant exposure range. Avibactam and ceftazidime do not inhibit the major renal or hepatic transporters in the clinically relevant exposure range. Avibactam is a substrate of human OAT1 and OAT3 transporters in vitro, which might contribute to the active uptake of avibactam. Ceftazidime does not interact with this active uptake of avibactam.

Nonclinical toxicology studies with avibactam were conducted in rats and dogs. Minimal toxicity was noted in rats or dogs with 4 or 13 week studies at doses up to 1000 mg/kg/day by the intravenous route with avibactam alone. Combination studies in rats and dogs at one

month with the combination of avibactam and ceftazidime did not demonstrate new toxicities or significantly more severe toxicity than with ceftazidime alone. Fertility, embryo-fetal development, and peri/post natal studies all showed minimal effects to the embryos at doses of avibactam alone up to 1000 mg/kg. Avibactam was not genotoxic.

6. EVALUATION OF CLINICAL EFFICACY

6.1. OVERVIEW

Two Phase 2 trials have been completed, one to assess the efficacy and safety of CAZ-AVI compared to imipenem-cilastatin in the treatment of subjects with cUTI (NXL104/2001), and the other to assess the efficacy and safety of CAZ-AVI + MTZ in the treatment of subjects with cIAI (NXL104/2002). In these trials, there was no pre-specification of any formal hypotheses for inferential testing, and statistical analysis is limited to descriptive data summaries. These summaries were provided for each of the primary and secondary variables.

Phase 3 trial in HABP/VABP is ongoing and the Phase 3 cUTI trial was recently completed. Data from the Phase 3 cUTI trial are not yet available. Preliminary experience from an open-label trial (Resistant Pathogen Study D4280C00006) in subjects with infections due to CAZ-NS pathogens has also been submitted. The combined Phase 3 cIAI trial (D4280C00001/5) has completed enrollment with top-line data now available (see Section 6.3.4); however, a final study report has not been officially submitted to the Agency and full review of these data are not expected for the completion of this NDA. Additionally, a literature review was conducted to assess the efficacy of ceftazidime in cIAI and cUTI and estimate the treatment effect restored by the addition of avibactam in infections caused by CAZ-R pathogens.

6.2. COMPLICATED URINARY TRACT INFECTIONS

6.2.1. Study Design

NXL104/2001 (Trial 2001) was a Phase 2, prospective, multicenter, investigator-blinded, randomized trial to evaluate the efficacy, safety, and tolerability of CAZ-AVI versus imipenem-cilastatin (IMI-CS) in the treatment of adults with cUTI. cUTI included acute pyelonephritis (AP), UTI in men or UTI associated with obstruction, foreign bodies, or urologic abnormalities. Eligible patients were adults aged ≥ 18 and ≤ 90 years, suspected of having cUTI due to gram-negative pathogens and judged by the investigator to require initial parenteral therapy and a need of no more than 7 to 14 days of antibacterial drugs and must not have received more than one dose of a potentially effective systemic antibacterial drug within 48 hours prior to the admission urine culture. Patients with an estimated creatinine clearance (CrCl) < 70mL/min by Cockcroft-Gault formula, or patients receiving either hemodialysis or peritoneal dialysis, were excluded.

Enrolled subjects were stratified based on the type of infection (AP or other cUTI without AP) and randomized 1:1 to CAZ-AVI 625 mg (500 mg ceftazidime + 125 mg avibactam) IV q8h over

30 minutes or IMI-CS 500 mg IV every 6 hours (q6h) over 30 minutes. The investigator determined switch to oral therapy (ciprofloxacin 500 mg PO q12h) was allowed after completion of at least four days of therapy. Overall, 135 subjects were randomized, including 68 in the CAZ-AVI group and 67 in the IMI-CS group. Approximately two-thirds of subjects enrolled in either treatment group had AP, including 44 (64.7%) subjects in the CAZ-AVI group and 41 (61.2%) subjects in the IMI-CS group.

The analysis populations are as follows and enumerated in Table 12.

Safety: All subjects who received at least one dose of study treatment.

mMITT (microbiological Modified Intent-To-Treat) population: Subjects who received at least 1 dose of study therapy and had a study qualifying pre-treatment urine culture containing $>10^5$ CFU/mL of at least one uropathogen.

ME (Microbiologically Evaluable) population includes subjects who:

- Had confirmed diagnosis, including clinical evidence of UTI and a positive admission urine culture defined as $>10^5$ CFU/mL (10^4 CFU/ml if bacteremic) of a uropathogen at baseline.
- Had received a total duration of antibacterial therapy of at least 7 days (IV alone or a combination of IV and oral therapy) or were classified as evaluable microbiological failures after completing at least 48 hours of IV study drug therapy.
- Did not have major protocol violations that would affect assessment of efficacy.
- Had a clinical and microbiological assessment at the Test of Cure (TOC) visit, including a quantitative urine culture.
- Did not receive concomitant antibacterial therapy with a non-study antibacterial drug to which the uropathogen was susceptible between the time of the admission culture and the TOC culture.
- Did not have the admission urine culture obtained more than 48 hours prior to the start of study therapy.
- Had >1 baseline pathogen susceptible to the IV study antibacterial drug.

Table 12: Trial 2001 Analysis Groups

	CAZ-AVI (N=69)	IMI-CS (N=68)	Total (N=137)
Safety	68 (98.6)	67 (98.5)	135 (98.4)
mMITT	46 (66.7)	49 (72.1)	95 (69.3)
ME	27 (39.1)	35 (51.5)	62 (45.3)

Comparability of treatment groups by baseline demographics are summarized in Table 13.

Table 13: Baseline Demographic Summary for Trial 2001—Safety Population

Characteristics		CAZ-AVI N=68	IMI-CS N=67	Overall N=135
Age	Mean (SE)	46.4 (18.2)	49.8 (18.3)	48.1 (18.3)
	Min	18	18	18
	Median	47.5	51	48
	Max	85	89	89
		n (%)	**n (%)**	**n (%)**
Age Group	Age under 65 years	57 (83.8)	54 (80.6)	111 (82.2)
	65 ≤ Age < 75	5 (7.4)	2 (3.0)	7 (5.2)
	Age 75 and over	6 (8.8)	9 (13.4)	15 (11.1)
	Missing	0 (0.0)	2 (3.0)	2 (1.5)
Sex	Female	51 (75.0)	49 (73.1)	100 (74.1)
	Male	17 (25.0)	18 (26.9)	35 (25.9)
Race	Asian	8 (11.8)	5 (7.5)	13 (9.6)
	Black / African American	2 (2.9)	5 (7.5)	7 (5.2)
	White	40 (58.8)	41 (61.2)	81 (60.0)
	Other	18 (26.5)	16 (23.9)	34 (25.2)
Ethnicity	Hispanic or Latino	18 (26.5)	18 (26.9)	36 (26.7)

CAZ-AVI: ceftazidime-avibactam; IMI-CS: imipenem-cilastatin

6.2.2. Clinical and Microbiological Response

The primary endpoint was microbiologic response in the ME population at the TOC Visit (5 to 9 days post-therapy). Table 14 presents the Applicant's primary efficacy analysis based on the microbiological response (reduction of the baseline uropathogen at entry from $>10^5$ CFU/mL to $<10^4$ CFU/mL) at the TOC visit in the ME population. Nineteen subjects (70.4%) in the CAZ-AVI group and 25 (71.4%) in the IMI-CS group had a favorable microbiological response (eradication). The observed difference in response rates was -1.1%, with the corresponding 95% exact confidence interval (CI) of (-27.2%, 25.0%).

Table 14: Microbiological Response at TOC—ME Population

	CAZ-AVI N=27 n (%)	IMI-CS N=35 n (%)	Observed Difference (95% CI)
Microbiological Outcome			
Eradication	19 (70.4)	25 (71.4)	-1.1 (-27.2, 25.0)
Persistence	8 (29.6)	10 (28.6)	
Persistence with acquisition of resistance	0	0	
Indeterminate	0	0	

CAZ-AVI: ceftazidime-avibactam; IMI-CS: imipenem-cilastatin

The ME population is a subgroup that excludes subjects based on post-randomization criteria that could potentially bias the results of the trial; therefore, an analysis of clinical and microbiological responses are also provided based on the mMITT population, defined as all randomized patients with baseline pathogens.

Table 15 presents three endpoints: microbiological, clinical, and clinical + microbiological outcome in the mMITT population. Thirty-one subjects (67.4%) in the CAZ-AVI group and 31 (63.3%) in the IMI-CS group had favorable microbiological response. The observed difference in response rates is 4.1% (95% CI: -16.1%, 23.8%). For the clinical response outcome, 37 (80.4%) subjects in the CAZ-AVI group achieved clinical cure at TOC while 36 (73.5%) of the subjects in the IMI-CS group achieved cure. The difference in the rate of clinical cure is 7.0% (95% CI: 11.6, 24.7). For the clinical and microbiological outcome, 29 (63.0%) of the subjects in the CAZ-AVI group and 25 (51.0%) of the subjects in the IMI-CS group achieved clinical and microbiologic response. The difference in the response rates is 12.0% (95% CI: -9.8%, 33.9%).

The clinical response rates observed for CAZ-AVI in this study are generally lower than the historical microbiological and clinical outcome rates at TOC associated with ceftazidime alone (approximately 90%). A discussion of studies used to estimate the historical evidence of drug effect in the treatment of cUTI with ceftazdime will be further discussed in Section 6.5.1.

Table 15: Clinical and Microbiological Response at TOC—mMITT Population

	CAZ-AVI N=46 n (%)	IMI-CS N=49 n (%)	Observed Difference (95% CI)*
Microbiological Response			
Eradication	31 (67.4)	31 (63.3)	4.1 (-16.1, 23.8)
Persistence	10 (21.7)	14 (28.6)	
Indeterminate	5 (10.9)	4 (8.2)	
Clinical Response			
Cure	37 (80.4)	36 (73.5)	7.0 (-11.6, 24.7)
Failure	5 (10.9)	9 (18.4)	
Indeterminate	4 (8.7)	4 (8.2)	
Clinical & Microbiological Response			
Cure + Eradication	29 (63.0)	25 (51.0)	12.0 (-9.8, 33.9)
Failure + Persistence or Indeterminate	17 (37.0)	24 (49.0)	

CAZ-AVI: ceftazidime-avibactam; IMI-CS: imipenem-cilastatin; *Exact 95% Clopper-Pearson confidence intervals

Table 16 presents the same endpoints based on a subgroup of mMITT subjects with CAZ-NS isolates. For this analysis, CAZ-NS included isolates with an MIC ≥ 8 mg/L for Enterobacteriaceae and ≥ 16 mg/L for *P. aeruginosa*. Nine subjects (64.3%) in the CAZ-AVI group and 10 (55.6%) in the IMI-CS group had favorable microbiological response (eradication). The observed difference in response rates was 8.7% (95% CI: -27.4%, 41.3%). For the clinical response outcome, 11 (78.6%) subjects in the CAZ-AVI group achieved clinical cure at TOC while 10 (55.6%) of the subjects in the IMI-CS group achieved clinical cure. The difference in the rate of clinical cure is 23.0% (95% CI: -14.0%, 51.2%). For the clinical and microbiological outcome, 8 (57.1%) of the subjects in the CAZ-AVI group and 7 (38.9%) of the subjects in the IMI-CS group achieved clinical and microbiologic response. The difference in the response rates is 18.3% (95% CI: -22.4%, 58.9%). For each of these endpoints, the differences between point estimates show that the response rate for CAZ-AVI is numerically higher than for IMI-CS. However, the wide confidence intervals around the treatment difference in the response rates show the degree of uncertainty in the results.

Table 16: Clinical Response and Microbiologic Outcome response at TOC—mMITT Population, Subjects with CAZ-NS Isolates

	CAZ-AVI N=14 n (%)	IMI-CS N=18 n (%)	Observed Difference (95% CI)*
Microbiological Outcome			
Eradication	9 (64.3)	10 (55.6)	8.7 (-27.4, 41.3)
Persistence	3 (21.4)	6 (33.3)	
Indeterminate	2 (14.3)	2 (11.1)	
Clinical Response			
Cure	11 (78.6)	10 (55.6)	23.0 (-14.0, 51.2)
Failure	2 (14.3)	5 (27.8)	
Indeterminate	1 (7.1)	3 (16.7)	
Clinical & Microbiological Outcome			
Cure + Eradication	8 (57.1)	7 (38.9)	18.3 (-22.4, 58.9)
Failure + Persistence or Indeterminate	6 (42.9)	11 (61.1)	

CAZ-AVI: ceftazidime-avibactam; IMI-CS: imipenem-cilastatin; *Exact 95% Clopper-Pearson confidence intervals

Table 17 shows the results for the clinical response by treatment and susceptibility to ceftazidime in the CAZ-AVI arm and imipenem in the IMI-CS arm. In this table, subjects in the IMI-CS arm whose baseline isolates were non-susceptible to imipenem can be considered a "putative placebo" group since these subjects received inadequate therapy. On the other hand, the addition of avibactam should restore some of the treatment effect of ceftazidime even if the baseline uropathogen is non-susceptible to ceftazidime. Note that the clinical cure and microbiological eradiation rate in the CAZ-AVI group in the mMITT population is 63.0% (see Table 15), whereas 1 of 2 (50.0%) subjects with inadequate therapy responded (see Table 17). The difference in response rates between the CAZ-AVI and IMI-CS groups given inadequate therapy is 13.0% (95% CI: -36.8%, 62.2%). Because only two subjects received inadequate therapy, the confidence interval is wide; therefore, with this degree of uncertainty, no meaningful inference can be made.

Table 17: Clinical Response and Microbiologic Outcome by Treatment and Susceptibility of Pathogen to Treatment Assignment—mMITT population

	CAZ-AVI N=46	IMI-CS N=49
Susceptible to	**Ceftazidime (N1=32)**	**Imipenem (N1=47)**
Cure + Eradication (n/N1 %)	21 (65.6)	24 (51.1)
Failure + Persistence or Indeterminate (n/N1 %)	11 (34.4)	23 (48.9)
Nonsusceptible to	**Ceftazidime (N1=14)**	**Imipenem (N1=2)**
Cure + Eradication (n/N1 %)	8 (57.1)	1 (50.0)
Failure + Persistence or Indeterminate (n/N1 %)	6 (42.9)	1 (50.0)

N1 = number of subjects with a baseline CAZ-NS uropathogen in the CAZ-AVI arm or imipenem-NS pathogen in the IMI-CS arm.

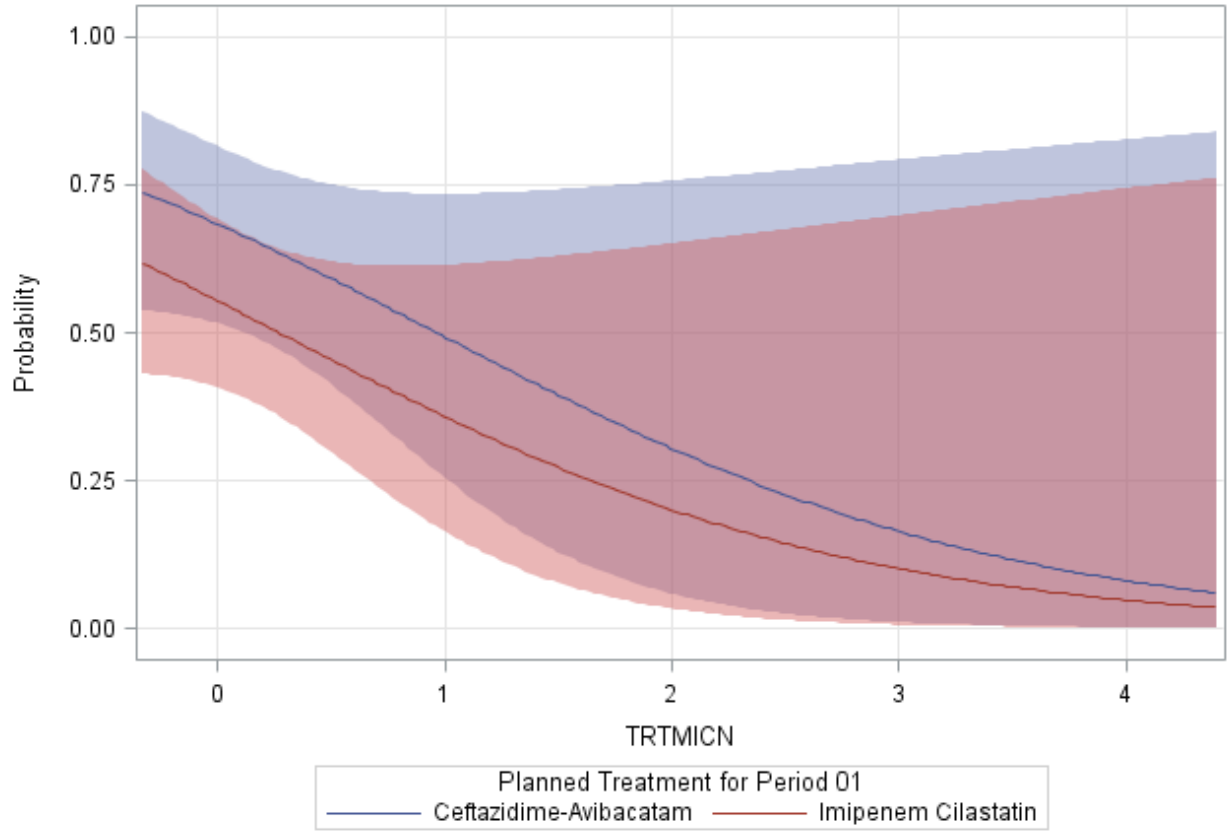
6.2.3. Other Supportive Analyses

6.2.3.1. Probability of Clinical Cure and its Relationship to MIC

A logistic regression was used to fit the logarithm of the odds of achieving clinical cure and microbiological eradication at the TOC visit by the MIC of the primary pathogen to the

corresponding assigned treatment (i.e. ceftazidime MIC in the CAZ-AVI group and imipenem MIC in the IMI-CS group). Figure 4 shows the curve of predictive probability of achieving clinical cure and microbiological eradication as a function of the MIC for each treatment group and its associated confidence bands. The graph shows that as the MIC gets higher, the probability of achieving clinical cure and microbiological eradication gets lower. However, the confidence bands about the predictive probability curve are wide. For example, the true predictive probability of cure at an MIC of 2 mg/L for CAZ-AVI can be anywhere within 5.8% to 75.6% with 95% confidence. Furthermore, the odds ratio between CAZ-AVI and IMP-CS is 1.741 with a 95% Wald confidence limit of (0.7218, 4.1993) (i.e., the odds that a subject achieves both clinical cure and microbiological eradication given that he/she is treated with CAZ-AVI is 1.741 larger than the odds compared of the outcome occurring in the IMP-CS group), but not statistically significant.

Figure 4: Trial 2001 - Predictive Probability for Achieving Clinical Cure and Microbiological Response as a Function of MIC (mg/L)



6.2.3.2. Per Pathogen Microbiological Response

Clinical cure and favorable microbiological response (eradication) at TOC were evaluated by uropathogen, as shown in Table 18. *E. coli* was the most common uropathogen, and was eradicated in 26/40 (65.0%) subjects in the CAZ-AVI group and 22/41 (53.7%) subjects in the IMI-CS group. The number of subjects with a uropathogen other than *E. coli* was extremely

small, prohibiting comparisons across treatment groups. In the CAZ-AVI group, *C. koseri* (one pathogen) was eradicated and *P. aeruginosa* (three pathogens) was not eradicated. In the IMI-CS group, *E. cloacae* (one pathogen), *M. morganii* (one pathogen) and *P. mirabilis* (one pathogen) were eradicated. There were two subjects with two or more baseline uropathogen: Subject 20413 had *C. koseri* and *E. coli* and Subject 40408 had *A. baumanii*, *A. junii*, and *P. aeruginosa.* There were three subjects, including two in the CAZ-AVI group and one in the IMI-CS group, that were flagged as members of the mMITT population, but with no listed uropathogen.

Table 18: Per Pathogen Response (Clinical Cure + Eradication)—mMITT Population

	CAZ-AVI (N= 46) n/N (%)	IMI-CS (N= 49) n/N (%)
Pathogen		
Acinetobacter baumanii	0/0	0/1 (0.0)
Acinetobacter junii	0/0	0/1 (0.0)
Citrobacter koseri	1/1 (100)	0/0
Enterobacter aerogenes	0/0	0/1 (0.0)
Enterobacter cloacae	0/0	0/1 (0.0)
Escherichia coli	26/40 (65.0)	22/41 (53.7)
Klebsiella oxytoca	0/0	1/1 (100)
Morganella morganii	0/0	1/1 (100)
Proteus mirabilis	0/0	1/1 (100)
Pseudomonas aeruginosa	0/3 (0.0)	0/1 (0.0)

Favorable microbiological response by uropathogen at TOC is shown in Table 19. As was noted in Table 18, *E. coli* was the most common uropathogen, and was eradicated in 8/14 (57.1%) cases in the CAZ-AVI group and 7/18 (43.8%) cases in the IMI-CS group at TOC.

Table 19: Per Pathogen Response (Clinical Cure + Eradication)—mMITT Population, Subjects with a CAZ-NS Uropathogen

	CAZ-AVI (N= 46) n/N1 (%)	IMP/CIL (N= 49) n/N1 (%)
Ceftazidime Non-Susceptible, N1	14	18
Escherichia coli	8/14 (57.1)	7/18 (43.8)
Enterobacter cloacae	0	0/1 (0.0)
Pseudomonas aeruginosa	0	0/1 (0.0)

Of the seven subjects with concurrent bacteremia at baseline in the mMITT population, two of three (66.7%) in the CAZ-AVI group (all *E. coli*) and two of four (50.0%) in the IMI-CS group had favorable microbiological outcomes at TOC.

Clinical cure (with or without microbiologic eradication) at TOC in subjects with a CAZ-NS uropathogen is shown in Table 20 by baseline diagnosis (with or without acute pyelonephritis) or by baseline pathogen.

Table 20: Clinical Cure at TOC by Baseline Diagnosis or Baseline Pathogen[*]—mMITT Population, Subjects with a CAZ-NS Uropathogen

	CAZ-AVI N=14 n/N1 (%)	IMI-CS N=18 n/N1 (%)
Baseline Diagnosis		
Acute pyelonephritis (AP)	5/6 (83.3)	4/8 (50.0)
Without AP	6/8 (75.0)	6/10 (60.0)
Baseline Pathogen		
Enterobacter cloacae	0/0 (0.0)	0/1 (0.0)
Escherichia coli	11/14 (78.6)	9/16 (56.3)
Pseudomonas aeruginosa	0/0 (0.0)	1/1 (100.0)
Total	11/14 (78.6)	10/18 (55.6)

[*]Baseline uropathogens and blood isolates that are also baseline uropathogens are included.

Although there was no significant discordance between microbiologic and clinical response in the ME population at TOC, including patterns among subjects by underlying diagnosis (i.e., pyelonephritis or other cUTI), there was a small subset of subjects who had ongoing bacterial growth from the urine in the absence of clinical signs or symptoms at TOC. None of the persistent isolates was associated with ≥ 4-fold increase in MIC (see Table 21), but half of these subjects later experienced clinical relapse at LFU.

Table 21: Subjects with Unfavorable Microbiological Responses (Persistence) and Favorable Clinical Responses at TOC—ME Population

Subject	Primary Diagnosis	Pathogen from urine	TOC MIC[*] (mg/L)	LFU MIC[*] (mg/L)	Clinical Outcome at LFU
CAZ-AVI group					
20213	Pyelonephritis	*E. coli*	0.12	0.12	Sustained cure
20313	Pyelonephritis	*E. coli*	0.12	0.06	Relapse
20407	Pyelonephritis	*E. coli*	0.12	0.12	Sustained cure
30203	cUTI	*E. coli*	0.25	0.12	Relapse
50105	cUTI	*P. aeruginosa*	4	4	Relapse
IMI-CS group					
20202	Pyelonephritis	*E. coli*	0.12	0.12	Sustained cure
20305	cUTI	*E. coli*	0.12	N/A	Sustained cure
20411	Pyelonephritis	*E. coli*	0.12	0.12	Sustained cure
30201	cUTI	*E. coli*	0.25	0.25	Sustained cure
40111	cUTI	*E. coli*	0.06	0.12	Relapse
40209	Pyelonephritis	*E. coli*	0.06	0.12	Relapse
40304	Pyelonephritis	*E. coli*	0.12	N/A	Relapse

[*]MIC of CAZ-AVI for the CAZ-AVI group and imipenem for the IMI-CS group.

6.3. Complicated Intra-Abdominal Infections

6.3.1. Study Design

NXL104/2002 (Trial 2002) was a prospective multicenter, double blind, randomized (1:1) trial to evaluate the safety, tolerability and efficacy of CAZ-AVI + MTZ compared with meropenem in the treatment of cIAI. The trial enrolled 203 subjects with cIAI that required surgical intervention plus parenteral antibacterial therapy for 5 to 14 days. Infections originating from the appendix, stomach or duodenum, small or large intestine, or biliary tree were included if they were associated with perforation and/or peritonitis or abscess. Non-perforating infections (e.g. infections limited to the hollow viscus, simple cholecystitis, simple appendicitis, ischemic bowel disease without perforation, acute suppurative cholangitis, and acute necrotizing pancreatitis) were specifically excluded. Subjects were excluded if they had received more than one dose (or more than 24 hours of perioperative prophylaxis) of a potentially effective systemic antibacterial therapy within the 72-hour period prior to study entry. Patients were also excluded if they had a baseline estimated CrCl < 50 mL/min by Cockcroft-Gault Formula or abnormal liver function tests. Elevations of aspartate aminotransferase (AST/SGOT) and/or alanine aminotransferase (ALT/SGPT) up to five times the upper limit of normal (ULN) were eligible if these elevations were acute and directly related to the infectious process being treated.

Enrolled subjects were stratified at entry based on APACHE II (Acute Physiology and Chronic Health Evaluation II) score (≤ 10 or > 10 but < 25) and randomized 1:1 to CAZ-AVI 2500 mg (2000 mg ceftazidime + 500 mg avibactam) IV q8h over 30 minutes + MTZ 500 mg IV q8h over 1 hour OR meropenem (1000 mg IV q8h over 30 minutes) + placebo MTZ (IV q8h over 1 hour).

The analysis populations that will be used in the subsequent review are as follows and enumerated in Table 22:

Safety: All subjects who received at least one dose of study treatment.

ME (Microbiologically Evaluable) includes all randomized subjects who:

- Had an appropriate diagnosis of intraperitoneal infection confirmed by operative findings and received an adequate course of therapy,
- Had sufficient information to determine clinical outcome at TOC, and
- Had at least one etiologic pathogen isolated from a clinically relevant specimen (peritoneal fluid, abscess fluid, peritoneal surface of infected organ prior to the incision of a hollow viscus, or blood culture in appropriate clinical setting) in the initial/pre-study culture that was susceptible to both study agents. Subjects with a polymicrobial infection where one or more pathogens were resistant in vitro to the study antibacterial drug were kept on study therapy at the discretion of the investigator, and were considered evaluable.

mMITT: All randomized subjects who received at least 1 dose of study drug and met the disease definition of IAI and had at least one bacterial pathogen identified at study entry regardless of susceptibility.

Table 22: Trial 2002 Analysis Groups

	CAZ-AVI N=102	Meropenem N=102	Total N=204
Safety	101 (99.0)	102 (100.0)	203 (99.5)
mMITT	85 (83.3)	89 (87.3)	174 (85.3)
ME	68 (66.7)	76 (7.5)	144 (70.6)

Approximately half of the subjects enrolled (49 [48.5%] in the CAZ-AVI group and 47 [46.1%] in the meropenem group) had appendix as the anatomic site of infection origin and most (approximately 90% overall, or 91 [90.1%] in the CAZ-AVI group and 91 [89.2%] in the meropenem group) had an open laparotomy. Other surgical interventions included laparoscopic procedures or percutaneous drainage. Comparability of treatment groups by baseline demographics is summarized in Table 23.

Table 23: Baseline Demographic Summary for Trial 2002—Safety Population

Characteristics		CAZ-AVI + MTZ N=101	Meropenem N=102	Overall N=203
Age	Mean (SE)	43.2 (16.0)	42.9 (18.1)	43.1 (17.0)
	Min	18	19	18
	Median	41	39	41
	Max	80	88	88
		n (%)	**n (%)**	**n (%)**
Age Group	Age under 65 years	92 (91.1)	87 (85.3)	179 (88.2)
	65 ≤ Age < 75	7 (6.9)	12 (11.8)	19 (9.4)
	Age 75 and over	2 (2.0)	3 (2.9)	5 (2.5)
Sex	Female	31 (30.7)	21 (20.6)	52 (25.6)
	Male	70 (69.3)	81 (79.4)	151 (74.4)
Race	American Indian / Alaskan Native	1 (1.0)	0 (0.0)	1 (0.5)
	Asian	32 (31.7)	23 (22.5)	55 (27.1)
	Black / African American	0 (0.0)	1 (1.0)	1 (0.5)
	White	56 (55.4)	65 (63.7)	121 (59.6)
	Other	12 (11.9)	13 (12.7)	25 (12.3)
Ethnicity	Hispanic or Latino	3 (3.0)	2 (2.0)	5 (2.5)

CAZ-AVI+MTZ: ceftazidime-avibactam+ metronidazole

6.3.2. Clinical Response

The primary endpoint was the clinical response in the ME Population at the test of cure/early follow-up (TOC/EFU) visit 2 weeks post-therapy. Investigator-determined and Sponsor-verified outcomes were also included in the analysis for the mMITT population. In the Applicant's primary analysis, 68/101 (67%) subjects in the CAZ-AVI group and 76/102 (75%) in the meropenem group were microbiologically evaluable. At the TOC visit, the proportion of subjects with favorable clinical response is 91.2% (62/68) in the CAZ-AVI group and 93.4% (71/76) in the meropenem group (see Table 24). The estimated difference in response rates

was -2.2% with the corresponding 95% exact confidence interval (calculated using Clopper-Pearson) -20.4% to 12.2%.

Table 24: Clinical Response at TOC/EFU—ME population

	CAZ-AVI n (%)	Meropenem n (%)	Observed Difference (95% CI)
ME Population	**N = 68**	**N = 76**	
Sponsor-verified favorable clinical response	62 (91.2)	71 (93.4)	-2.2 (-20.4, 12.2)
Sponsor-verified clinical failure	15 (17.7)	10 (11.2)	

The ME population excludes subjects based on post-randomization criteria that could potentially bias the results of the trial; therefore, an analysis of clinical response is also provided based on the mMITT population, which is interpretable and protected by randomization. Although by definition, the mMITT excludes subjects without a pathogen isolated at baseline, this analysis set had 85/101 (83.3%) subjects in the CAZ-AVI group and 89/102 (87.3%) subjects in the meropenem group (Table 22). Within the mMITT, the Sponsor-verified favorable clinical response was achieved in 70/85 (82.4%) in the CAZ-AVI group and 79/89 (75%) in the meropenem group with a difference in clinical response of -6.4% (95% CI: -18.0, 5.2) (Table 25).

Table 25: Clinical Response at TOC/EFU by APACHE II Score Category, Stratum—mMITT Population

	CAZ-AVI n (%)	Meropenem n (%)	Observed Difference (95% CI)
mMITT Population	**N = 85**	**N = 89**	
Sponsor-verified favorable clinical response	70 (82.4)	79 (88.8)	-6.4 (-18.0, 5.2)
Sponsor-verified clinical failure	15 (17.7)	10 (11.2)	
APACHE Score Category			
0-5	37/42 (88.1)	43/48 (89.6)	
6-10	20/29 (68.0)	23/25 (92.0)	
11-15	10/10 (100.0)	13/15 (86.7)	
16-19	3/4 (75.0)	0/1 (0.0)	
APACHE Stratum			
≤ 10	57/71 (80.3)	66/73 (90.4)	
> 10 but < 25	13/14 (92.9)	13/16 (81.3)	

In the subgroup of subjects with infections caused by CAZ-NS pathogens (Table 26), the Sponsor-verified favorable clinical response is 27/30 (90.0%) in the CAZ-AVI group and 19/23 (82.6%) in the meropenem group with a treatment response difference of 7.4% (95%CI: -15.3, 30.0). In comparing the results for subjects in the mMITT population, CAZ-AVI has an overall treatment response that is numerically lower than meropenem (Table 25), while in the subgroup of subjects infected with CAZ-NS pathogens, CAZ-AVI has a numerically higher treatment response than meropenem (Table 26). It is not clear why the CAZ-AVI response rate is lower than meropenem in the mMITT population.

Table 26: Clinical Response at TOC/EFU—mMITT Population, Subjects with a CAZ-NS Pathogen

	CAZ-AVI n (%)	Meropenem n (%)	Observed Difference (95% CI)
CAZ-NS Population	**N = 30**	**N = 23**	
Sponsor-verified clinical cure	27 (90.0)	19 (82.6)	7.4 (-15.3, 30.0)
Sponsor-verified clinical failure	3 (10.0)	4 (17.4)	

Among subjects assigned to CAZ-AVI with a CAZ-susceptible pathogen, 43 of 55 (78.2%) had a Sponsor-verified favorable clinical response (Table 27). For subjects with CAZ-NS pathogens, the Sponsor-verified clinical response rate was 27/30 (90.0%). On the other hand, in subjects given inadequate therapy (i.e., those randomized to meropenem, but whose baseline pathogen was not susceptible to meropenem), the Sponsor-verified clinical response rate was 3/4 (75.0%, Table 27). The difference in response rate between those given CAZ-AVI (82.4% in mMITT population, Table 25) and inadequate therapy (75.0% with meropenem for non-susceptible isolate) is 7.4% (95% CI: -18.4, 60.9). Note that the number of subjects is limited to make any meaningful and valid inference.

Table 27: Clinical Response at TOC/EFU by Treatment Group and Susceptibility of Pathogen to Treatment Assignment—mMITT population

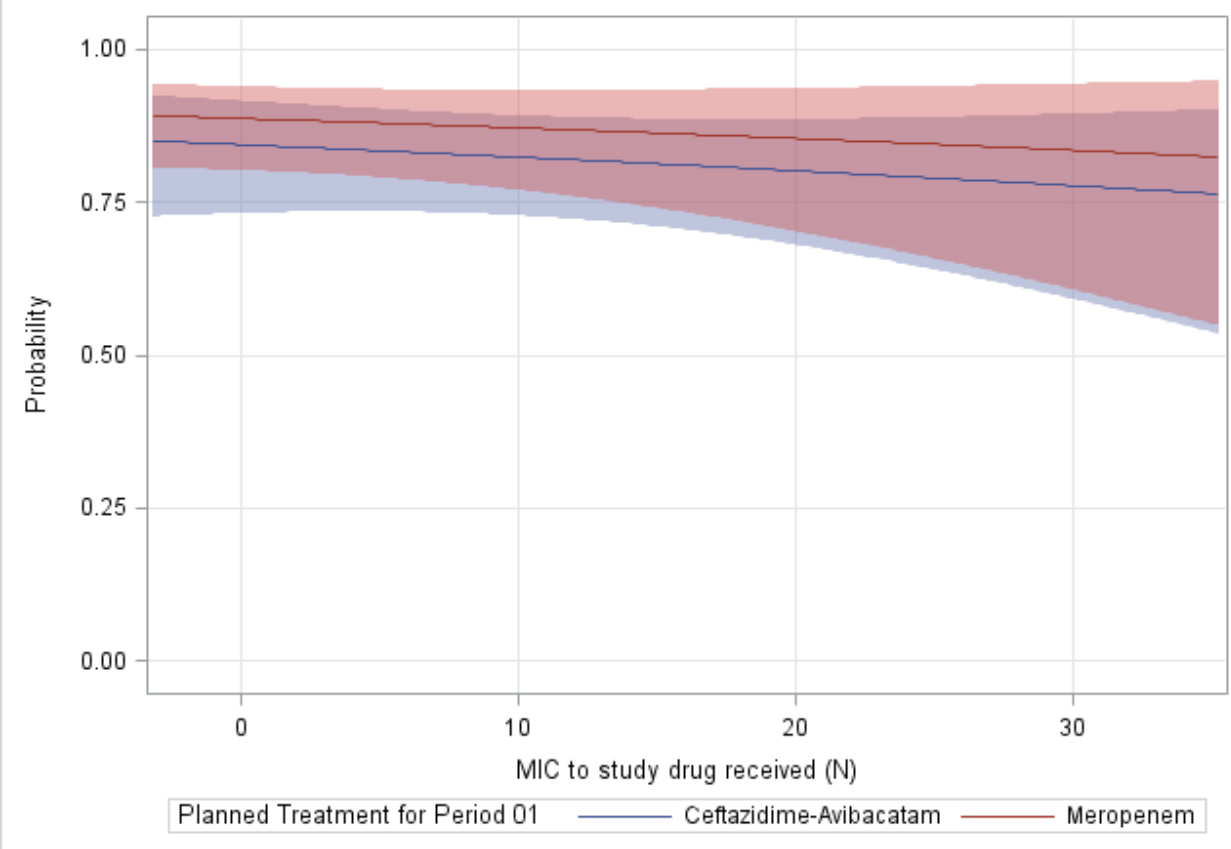
	CAZ-AVI N = 85 n (%)	Meropenem N = 89 n (%)
Susceptible to	**Ceftazidime**	**Meropenem**
Cure	43 (78.2)	76 (89.4)
Failure	5 (9.1)	9 (10.6)
Indeterminate	7 (12.7)	0
Nonsusceptible to	**Ceftazidime**	**Meropenem**
Cure	27 (90.0)	3 (75.0)
Failure	2 (6.7)	1 (25.0)
Indeterminate	1 (3.3)	0

6.3.3. Other Supportive Analyses

6.3.3.1. Probability of Clinical Cure and its Relationship to MIC

A logistic regression was used to fit the logarithm of the odds of achieving clinical cure at the TOC as a function of MIC by the assigned treatment (i.e., ceftazidime MIC in the CAZ-AVI group and meropenem MIC in the meropenem group). Figure 5 shows that at TOC, the predictive probability of achieving clinical cure does not change as the MIC gets higher. Furthermore, and as expected from Table 25, the odds ratio between CAZ-AVI and meropenem is less than 1 (OR = 0.689) with 95% Wald confidence interval of (0.2751, 1.7256). Although not statistically significant, the odds ratio increases at late follow-up (LFU) to 0.9877 (0.3995, 2.4418).

Figure 5: Trial 2002 - Predictive Probability for Achieving Clinical Cure and Microbiological Response as a Function of MIC (mg/L)



6.3.3.2. Per Pathogen Microbiological Response

More than a third (36.8%) of the subjects in the mMITT population had polymicrobial infections (64/174). The most common pathogens identified were *E. coli, K. pneumoniae, S. aureus, P. aeruginosa, B. fragilis and E. faecium* (Table 28).

For *E. coli*, the microbiological response (presumed eradication) rate was favorable for 48/55 (87.2%) of isolates in the CAZ-AVI group and 52/58 (89.7%) of isolates in meropenem group. For all other gram-negative aerobic isolates, favorable responses were seen in the CAZ-AVI group (21/26) and also in the meropenem group (30/31).

Table 28: By-Pathogen Response (Presumed Eradication)—mMITT Population

	CAZ-AVI N = 85 n/N1	Meropenem N = 89 n/N1
Gram Positive Aerobic Pathogens	22/24	22/22
Enterococcus avium	1/2	0/0
Enterococcus faecalis	5/5	3/3
Enterococcus faecium	3/4	4/4
Staphylococcus aureus	5/5	8/8
Staphylococcus capitis	1/1	0/0
Staphylococcus lugdunensis	1/1	0/0
Streptococcus Group C	1/1	0/0
Streptococcus bovis	1/1	0/0
Streptococcus constellatus	1/1	0/0
Streptococcus intermedius	1/1	1/1
Streptococcus pneumoniae	1/1	0/0
Streptococcus salivarius	1/1	0/0
Gram Negative Aerobic Pathogens	69/81	82/89
Acinetobacter baumannii	1/1	2/2
Campylobacter gracilis	0/1	0/0
Citrobacter amalonaticus	0/1	0/0
Enterobacter cloacae	1/1	4/4
Escherichia coli	48/55	52/58
Escherichia hermannii	0/1	0/0
Klebsiella oxytoca	2/2	2/2
Klebsiella pneumoniae	6/7	10/10
Proteus mirabilis	1/2	1/1
Providencia stuartii	1/1	0/0
Pseudomonas aeruginosa	6/6	5/5
Pseudomonas species	1/1	0/0
Pseudomonas stutzeri	1/1	0/0
Stenotrophomonas maltophilia	1/1	0/0
Anaerobic Pathogens	20/27	15/20
Bacteroides caccae	2/2	0/2
Bacteroides distasonis	1/1	0/1
Bacteroides eggerthii	1/1	0/1
Bacteroides fragilis	3/7	3/7
Bacteroides thetaiotaomicron	1/1	2/1
Bacteroides uniformis	2/2	1/2
Clostridium clostridioforme	1/1	1/1
Clostridium perfringens	2/2	0/2
Clostridium ramosum	3/3	1/3
Finegoldia magna	1/1	0/1
Fusobacterium necrophorum	0/1	0/1
Fusobacterium varium	1/1	0/1
Peptostreptococcus micros	1/1	1/1
Peptostreptococcus prevotii	0/1	1/1
Prevotella intermedia	1/1	0/1
Prevotella melaninogenica	0/1	0/0

Favorable microbiological response by baseline pathogen at TOC is shown in Table 29. *E. coli* was eradicated in 20/22 (90.1%) cases in the CAZ-AVI group and 15/17 (93.8%) cases in the meropenem group at TOC. Eradication rate in either subgroup is relatively high.

Table 29: By-Pathogen Response (Presumed Eradication) at TOC in Subjects with a CAZ-NS Pathogen

	CAZ-AVI N = 85 n/N1	Meropenem N = 89 n/N1
Ceftazidime non-susceptible	29	21
Acinetobacter baumannii	1/1	1/1
Citrobacter braakii	0	1/1
Enterobacter cloacae	0	0/1
Escherichia coli	20/22	15/16
Klebsiella pneumoniae	3/3	2/2
Proteus mirabilis	1/1	0
Providencia stuartii	1/1	0
Pseudomonas aeruginosa	1/1	1/1

6.3.4. Preliminary Phase 3 cIAI Trial Results

The Phase 3 trial in subjects with cIAI (from combined protocols D4280C00001/5, also referred to as RECLAIM) have been recently unblinded and preliminary analyses conducted by the Applicant are now available. As previously noted, the full results have not yet been submitted to the FDA for review and are not expected for completion of this NDA.

RECLAIM was a randomized, multi-center, double-blind trial to assess the noninferiority of CAZ-AVI (2000 mg/500 mg, q8h) plus MTZ (0.5 g q8h) versus meropenem (1 g q8h) in the treatment of cIAI. The primary endpoint was the clinical cure at TOC, 28 to 35 days after randomization, in subjects who have at least one identified pathogen (mMITT population) and the noninferiority margin was 10%. Patients with an estimated baseline CrCl ≤ 30 mL/min were excluded (note, patients were excluded with CrCl < 50 mL/min in Trial 2001 and < 70mL/min in Trial 2002).

A total of 1066 subjects were randomized from 30 countries. For the primary endpoint of clinical cure at TOC in the mMITT population, the lower and upper bounds of the 95% confidence interval were -8.64% and 1.58%, respectively. However, subgroup analyses indicated that cIAI patients with moderate renal impairment (CrCl > 30 to ≤ 50 mL/min) at baseline in the CAZ-AVI group had a lower clinical cure rate (14/31, 45%) compared to patients treated with meropenem (26/35, 74%). In subjects with normal renal function or mild renal impairment at baseline, the clinical cure rates were similar across treatment arms and higher than the cure rate for the corresponding moderately impaired subgroup (Table 30).

Table 30: Clinical Cure at TOC by Baseline Renal Function Category—mMITT Population, RECLAIM Trial

Baseline renal function subgroup	Number of patients with clinical cure/ Total number of patients (%)	
	CAZ-AVI + MTZ	Meropenem
Normal function / mild impairment (CrCl > 50 mL/min)	322/379 (85%)	321/373 (86%)
Moderate impairment at baseline (CrCl > 30 to ≤ 50 mL/min)	14/31 (45%)	26/35 (74%)

In addition to the clinical cure rates described above, among subjects with moderate renal impairment, there was also a numerical imbalance of deaths between the treatment groups (8 deaths in the CAZ-AVI subgroup compared to 3 deaths in the meropenem subgroup). Of note, deaths were also assessed as non-responders when the death occurred before the outcome assessment.

For comparison, clinical cure rates from Trial 2002 (the Phase 2 cIAI trial) by baseline renal function category are shown in Table 31. While the clinical cure rates in the mMITT population with mild renal impairment were numerically lower than those for subjects with normal renal function (77.3% CAZ-AVI, 85.7% meropenem), the number of subjects with mild renal impairment and clinical failure is small (5 CAZ-AVI and 3 meropenem). In Trial 2001 (the Phase 2 cUTI trial), microbiological eradication rates in the mMITT population with mild renal impairment were lower in the CAZ-AVI group (55.6% CAZ-AVI, 72.7% IMI-CS), whereas clinical cure rates were higher in the CAZ-AVI group (88.9% CAZ-AVI, 63.6% IMI-CS). In the ongoing Phase 3 Resistant Pathogen Study (D4280C00006), only two cIAI subjects have been enrolled with impaired renal function (one with mild and one with moderate renal impairment). Both subjects received BAT and were clinical failures at TOC.

Table 31: Clinical Cure Rate at TOC, by Baseline Renal Function Category—mMITT Population, Trial 2002

Baseline renal function subgroup	Number of patients with clinical cure/ Total number of patients (%)	
	CAZ-AVI + MTZ	Meropenem
Normal function (CrCl > 80 mL/min)	50/60 (83.3)	57/64 (89.1)
Mild impairment at baseline (CrCl > 50 to ≤ 80 mL/min)	17/22 (77.3)	18/21 (85.7)
Moderate impairment at baseline (CrCl > 30 to ≤ 50 mL/min)	0/0	4/4 (100.0)

A potential explanation provided by the Applicant of these findings includes the lack of timely dose adjustment for some moderately impaired subjects whose CrCl improved rapidly after baseline. The baseline assessment of CrCl did not take account of how the patient's renal function might change post-baseline. The resulting lag between recovery of renal function and

dose adjustment in some subjects may have contributed to underexposure and impacted their clinical outcome. Although the proportion of moderately impaired subjects whose estimated CrCl improved to > 50 mL/min in the first two days post-baseline was similar between the treatment arms, the baseline dose adjustment for CAZ-AVI for moderate renal impairment entails a 66% reduction in total daily dose of ceftazidime (from 6 g/day to 2 g/day) compared to a 33% reduction for meropenem (from 3 g/day to 2 g/day). At Day 3, however, in those who remained in the study and from whom PK sampling could be obtained, there was no evidence of inadequate exposure of patients in the CAZ-AVI moderately impaired subgroup. An analysis of the relationship between exposure and clinical outcome, including subjects whose renal function recovered at Day 3, is not available. As with any subgroup analysis, similarities in other baseline factors, sample size of the subgroup, as well as multiplicity in statistical testing should be taken into account.

6.4. POOLED ANALYSES

In the pooled analysis, interim data from the ongoing Resistant Pathogen Study (D4280C00006), was included to provide additional supportive information for the clinical efficacy of CAZ-AVI against CAZ-NS pathogens. The study is a Phase 3 multinational, multicenter, randomized, open-label study in adult subjects with cIAI and cUTI caused by CAZ-NS gram-negative pathogens. Subjects are stratified for entry diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world) and randomized 1:1 to CAZ-AVI or best available therapy (BAT) groups.

The dosage of CAZ-AVI used was 2.5 g (2.0 g ceftazidime + avibactam 0.5 g) IV q8h infused over 2h). BAT was chosen, as a single antibacterial drug is unlikely to cover all possible resistance mechanisms. As of the data cutoff, all subjects randomized to the BAT group have received a carbapenem (e.g., imipenem, meropenem) alone or in combination with colistin or ciprofloxacin. Subjects are to receive a minimum of five days and a maximum of 21 days of antibacterial therapy.

At the time of the data cutoff, the mMITT population included four subjects with cIAI and 44 subjects with cUTI. Table 32 shows the interim results of this study in terms of the infection type. The results show a similar trend in treatment effect as observed in Table 18 (i.e., the clinical response rate for CAZ-AVI is numerically higher than the comparators, but the point estimate of the treatment effect has substantial uncertainty as expressed by the wide confidence interval).

Table 32: Resistant Pathogen Study D4280C00006: Clinical Response at TOC/EFU by Infection Type—Interim Data

	CAZ-AVI N = 22	Comparators N = 26	Observed Difference (95% CI)
cUTI	**N1 = 21**	**N1 = 23**	
Clinical cure (n/N1%)	19 (90.5)	18 (78.3)	12.2 (-13.8, 36.0)
Clincal failure or Indeterminate (n/N1%)	2 (9.5)	5 (21.7)	
cIAI	**N1 = 1**	**N1 = 3**	
Clinical cure (n/N1%)	1 (100.0)	1 (33.3)	66.7 (-42.7, 98.2)
Clincal failure or Indeterminate (n/N1%)	0	2 (66.7)	
Pooled cUTI and cIAI	**N1 = 22**	**N1 = 26**	
Clinical cure (n/N1%)	20 (90.9)	19 (73.1)	17.8 (-8.2, 40.3)
Clincal failure or Indeterminate (n/N1%)	2 (9.9)	7 (26.9)	

Note that the Resistant Pathogen Study used CAZ-AVI at the proposed dose for cUTI (2.5 g [2.0 g ceftazidime + avibactam 0.5 g]) q8h as a 2-hour IV infusion), while the dose in Trial 2001 was 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) q8h administered as a 30-minute IV infusion; therefore, the combined preliminary cUTI results from the Resistant Pathogen Study and the results of Trial 2001 can be considered a conservative estimate of CAZ-AVI treatment response in cUTI at the 2.5 g dose.

Table 33 shows the observed clinical response and the posterior predictive probability of clinical response (cure) in the pooled studies (Trial 2001, Trial 2002, D4280C00006). In the pooled mMITT population, the observed clinical response rate of CAZ-AVI is 83.6% and the combined comparator response rate is 81.7% with a treatment difference of 1.3% (95% CI: -6.1%, 10.1%). The posterior predictive probability of clinical cure for the CAZ-AVI group is 86.2% and for the combined comparators that probability is 85.0%. The difference in posterior predictive probabilities is 1.1 (95% credible interval: -6.6, 8.8) which is narrower than the continuity corrected confidence interval of the difference in proportion. The posterior predictive probability is obtained using a shrinkage estimator to shrink the treatment response of each subgroup toward an overall mean. The amount of shrinkage is determined by the subgroup size and the estimated between group variability. Then using Bayesian estimation with shrinkage priors (i.e., priors that are centered at zero) for each of the four subgroups (CAZ-AVI for cUTI, CAZ-AVI for cIAI, Comparators for cUTI and Comparators for cIAI), the shrinkage estimates of the proportion in each of the subgroups are obtained. Note that the credible intervals of these estimates are narrower, hence more precise, than the difference in proportions with continuity correction.

Furthermore, since the Resistant Pathogen Study is composed mainly of subjects with cUTI, the pooled result reflects results that were similar to those observed in Trial 2001 and Trial 2002; namely, that CAZ-AVI has a numerically higher treatment response than its comparators (IMI-CS and BAT) in cUTI, but it has a numerically lower treatment response than its comparators (meropenem and BAT) in cIAI.

Table 33: Pooled Studies (Trial 2001, Trial 2002, D4280C00006): Clinical Response at TOC/EFU by Infection Type

	CAZ-AVI n (%)	Comparators n (%)	Diff (95% CI / Cred Int)
Pooled mMITT Population	**N = 153**	**N = 164**	
Observed clinical cure	127 (83.0)	134 (81.7)	1.3 (-7.6, 10.1)
Posterior predictive probability of clinical cure	86.2	85.0	1.1 (-6.6, 8.8)
Pooled cUTI Population	**N1 = 67**	**N1 = 72**	
Observed clinical cure	56 (83.6)	54 (75.0)	8.6 (-6.1, 22.6)
Posterior predictive probability of clinical cure	86.7	79.5	7.1 (-5.0, 19.5)
Pooled cIAI Population	**N1 = 86**	**N1 = 92**	
Observed clinical cure	71 (82.6)	80 (87.0)	-4.4 (-16.0, 7.0)
Posterior predictive probability of clinical cure	85.9	89.5	-3.5 (-13.2, 5.6)

As a cautionary note, pooling observations assumes exchangeability of subjects (i.e., the sequence subjects in each subgroup determined by study, treatment group or infection type), are assumed to have similar characteristics and were given comparable care. The plausibility of the assumption of exchangeability of subgroups should always be investigated. For example, the dose used in Trial 2001 is different from the other two studies (Trial 2002 and the Resistant Pathogen Study); therefore, a separate analysis was done with only the data from the latter two studies (Table 34). The results show that the point estimates are consistent with what was observed in Table 33. The only difference is the wider confidence intervals due to reduced sample sizes.

Table 34: Pooled Studies (Trial 2002, D4280C00006): Clinical Response at TOC/EFU by Infection Type

	CAZ-AVI n (%)	Comparators n (%)	Diff (95% CI / Cred Int)
Pooled mMITT Population			
Observed clinical cure	90 (84.1)	98 (85.2)	-1.1 (-11.4, 9.0)
Posterior predictive probability of clinical cure	87.4	88.3	-0.9 (-9.3, 7.3)
Pooled cUTI Population			
Observed clinical cure	19 (90.5)	18 (78.3)	12.2 (-13.8, 36.0)
Posterior predictive probability of clinical cure	91.4	84.4	7.0 (-8.6, 24.7)
Pooled cIAI Population			
Observed clinical cure	71 (82.6)	80 (87.0)	-4.4 (-16.0, 7.0)
Posterior predictive probability of clinical cure	86.0	89.5	-3.4 (-12.9, 5.4)

Lastly, the following investigation is related to the differential treatment response of CAZ-AVI in subjects with ceftazidime-susceptible and non-susceptible pathogens shown in Table 35. The pooled data show the same results that the treatment response of CAZ-AVI in subjects whose infection is caused by CAZ-S pathogens is lower than the treatment response of CAZ-AVI in those subjects with non-susceptible pathogens. Furthermore, the treatment response of CAZ-AVI is better than the comparators in the group of subjects with non-susceptible pathogens. In the CAZ-NS population, the treatment effect is 16.2% (95% CI: 1.4%, 30.3%). Its corresponding difference in median posterior probability using shrinkage estimates is 13.2 (95% credible interval: 1.5, 26.4). In the CAZ-S population, the treatment difference between CAZ-AVI and comparators (meropenem, imipenem, BAT) is -9.4% (-20.9%, 2.0%). The corresponding difference in median posterior probability is -7.4 (95% credible interval: -17.4, 1.4).

Table 35: Pooled Studies (Trial 2001, Trial 2002, D4280C00006): Clinical Response at TOC/EFU by Susceptibility to Assigned Treatment

	CAZ-AVI n (%)	Comparators n (%)	Observed Diff (95% CI / Cred Int)
Pooled CAZ-NS Population	**N1 = 66**	**N1 = 67**	
Clinical cure	58 (87.9)	48 (71.6)	16.2 (1.4, 30.3)
Posterior predictive probability of clinical cure	90.1	76.7	13.2 (1.5, 26.4)
Pooled CAZ-S Population	**N1 = 87**	**N1 = 97**	
Clinical cure	69 (79.3)	86 (88.7)	-9.4 (-20.9, 2.0)
Posterior predictive probability of clinical cure	83.4	90.9	-7.4 (-17.4, 1.4)

6.5. META-ANALYSES OF CEFTAZIDIME TREATMENT RESPONSE IN cUTI AND cIAI FROM HISTORICAL STUDIES

6.5.1. Historical Studies in cUTI

The Applicant provided a review of literature in order to evaluate the efficacy of ceftazidime alone in adult patients with cUTI. The review identified 400 articles (112 from PubMed, 87 from Ovid, 153 from Cochrane, and 48 from ClinicalTrials.gov). From this initial pool of articles, 160 unique search results were assessed and 33 cUTI studies were included in the Sponsor review. The criteria to include the article in the meta-analysis of the efficacy of ceftazidime in cUTI were as follows:

1. Study was a clinical trial in adult human subjects (i.e., exclude in vitro, animal, or pediatric studies)
2. Study included a ceftazidime group and a control/comparator group. (NOTE: the comparator group may be best available therapy (BAT) or similar group representing a variety of comparative treatments)
    a. Combination therapy of ceftazidime administered with another antibiotic qualified as a "ceftazidime group"
    b. A combination product (eg, ceftazidime plus a β-lactamase inhibitor, such CAZ-AVI) did not qualify as a "ceftazidime group"
3. Study included subjects with UTI that is defined as complicated or potentially contains subjects with cUTI
4. Study was prospective and randomized
5. Total 24-hour dose of ceftazidime was ≥ 1000 mg for presumed cUTI (consistent with the minimum labeled dosing for cUTI) (Fortaz® Package Insert, 2010)
    a. Lower doses were acceptable for patient populations with renal impairment
    b. Acceptable if study indicated the use of approved dosing without stating the specific dose
6. Microbiological and/or clinical outcomes were reported for ceftazidime efficacy in presumed cUTI
7. Ceftazidime/comparator results in presumed cUTI were presented such that sufficient information exists to extract or extrapolate the numerators and denominators for each relevant data point.

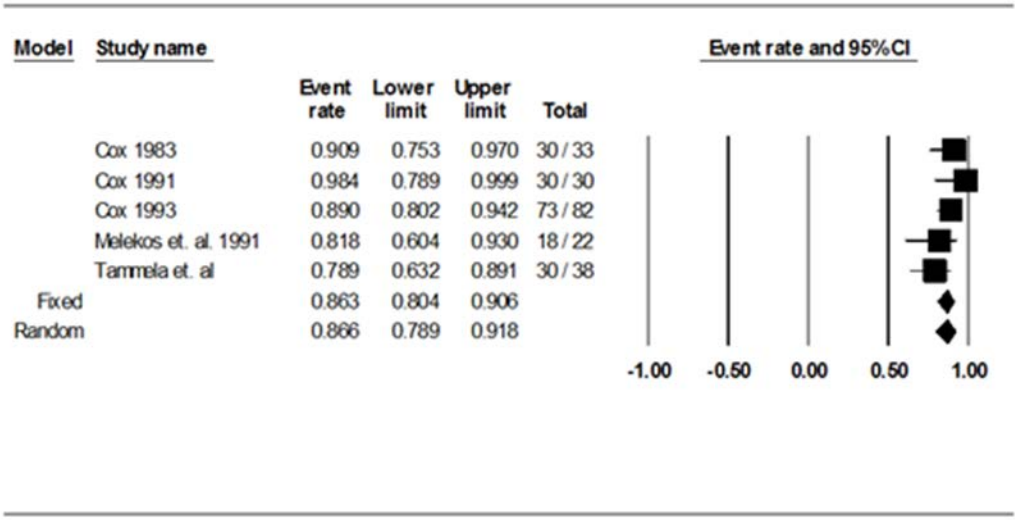
The meta-analysis was conducted using the DerSimonian & Laird random effects method. Ceftazidime was associated with approximately 89.1% (90% CI: 85.0, 93.2%) favorable microbiological response rates at TOC and 92% (90.4% CI: 85.5, 95.4%) favorable clinical outcome rates at TOC in the historical cUTI studies in a population that is similar to a ME population (Table 36). An analogue random effects formulation using Bayesian estimation is also computed (i.e., each response is parametrized with an overall mean and a random effect associated with each study that is assumed to be normally distributed with mean zero and some variance). The Dirichlet process prior provides a more robust estimate when the normality assumption does not hold and if there is perceived non-exchangeability in the data. Overall, based on this meta-analysis of controlled trials, ceftazidime was associated with approximately 90% (90% CI: 85.9, 93.1%) favorable microbiological response rates at TOC and 92% (90% CI: 88.8, 95.9%) favorable clinical outcome rates at TOC in the historical cUTI studies in a population that is similar to a ME population. The corresponding Bayesian estimate of favorable clinical response, using the Dirichlet process prior, is 91.9% (95% CI: -81.3, 98.1). For the microbiological response, the estimate is 88.6% with a 95% credible interval of (80.5, 95.3). In general, the results of the meta-analysis gives a higher favorable rate for ceftazidime in both clinical and microbiological responses than what was observed in Trial 2001 (see Table 15).

To better gauge the clinical cure and microbiological eradication rate of ceftazidime in historical trials, an approximation is used by taking the proportion that is the minimum of the observed clinical cure rate and the observed microbiological eradication rate. Furthermore, trials where cUTI subjects are a subgroup of the ME population are excluded. This narrows down the list of studies to five (Figure 6) and of the combined clinical cure and microbiological eradication rate using DerSimonian and Laird random effects estimate is 86.6% with a 95% confidence interval of (78.9, 91.8). Note that this response rate is still higher than what was observed in Trial 2001.

Table 36: Meta-Analysis of Historical Trials of Ceftazidime in the Treatment of cUTI

	DerSimonian & Laird	Bayesian Flexible Random effects	
		Normal Prior	Dirichlet Process Prior
	Est (95% Conf. Int)	Est (95% Credible Int)	Est (95% Credible Int)
Favorable clinical response	90.4 (85.5, 95.4)	91.1 (78.8, 97.4)	91.9 (81.3, 98.1)
Favorable microbiological response	89.1 (85.0, 93.2)	88.0 (80.4, 93.6)	88.6 (80.5, 95.3)

Figure 6: Forest Plot of Historical Trials with Ceftazidime in the Treatment of cUTI



Note that the analysis population used in the analysis is the ME population, which removes patients who had major protocol deviations and who did not have post-therapy evaluations. These post-randomization exclusions remove the protection from bias provided by randomization. Furthermore, most of the studies involved are open label which could potentially bias the results to reflect toward the goal of the study regardless of how honest the intentions were of the investigator.

6.5.2. Historical Studies in cIAI

The criteria to include the articles in the meta-analysis of the efficacy of ceftazidime in cIAI were as follows:

1. Study was a clinical trial in adult human subjects (i.e., excluded in vitro, animal, pediatric studies)
2. Study included a ceftazidime group and a control/comparator group (NOTE: the comparator group may have been a “best available therapy” or similar group representing a variety of comparative treatments)
    a. Combination therapy of ceftazidime administered with another antibiotic (e.g., MTZ) qualified as a “ceftazidime group”
    b. A combination product (e.g., ceftazidime plus a β-lactamase inhibitor, such CAZ-AVI) did not qualify as a “ceftazidime group”
3. Study included subjects with intra-abdominal infection (IAI) that is defined as complicated or potentially contains subjects with complicated IAI
4. Study was prospective and randomized
5. Total 24-hour dose of ceftazidime was ≥ 6 g for presumed cIAI
    a. Acceptable if study indicated the use of approved dosing without stating the specific dose
6. Clinical and/or microbiological outcomes were reported for ceftazidime efficacy in presumed cIAI

7. Ceftazidime/comparator results in presumed cIAI were presented such that sufficient information exists to extract or extrapolate the numerators and denominators for each relevant data point.

The above search yielded two cIAI articles where the ceftazidime dosage was 6 g IV daily and administered in three divided doses. The comparator regimen in both articles was tobramycin plus clindamycin. In one study, ceftazidime was administered with adjunctive clindamycin (Bubrick et al, 1990); in the other, ceftazidime was administered as monotherapy (Simmen et al, 1989). Neither the duration of therapy nor the time points at which favorable response was assessed was defined in either study. The analysis population is similar to the ME population based on the microbiology and exclusions made.

Table 37: Articles Used to Evaluate the Efficacy of Ceftazidime Alone in Patients with cIAI

Citation	Dose	Clinical Assessment	Ceftazidime	Comparator
Bubrick et al, 1990	2 g IV q8h + clindamycin 900 mg IV q8h	Time point not defined	31/34	30/34
Simmen et al, 1989	2 g IV TID + 600 mg clindamycin	Time point not defined	26/33	16/33

Based on these studies, ceftazidime was associated with approximately 86% (90% CI: 76.0, 96.1%) favorable clinical response rates at post-therapy assessment time points in the cIAI studies in a population that is similar to an ME Population.

6.6. LIMITATIONS IN THE ANALYSES

There are several limitations in the summary of these results based on individual trials, pooled analysis and the supportive meta-analyses. In the Phase 2 trials for cUTI and cIAI, there were no pre-specified formal hypotheses for any inferential testing; therefore, statistical analyses are based only on descriptive data summaries. In the pooled analysis as presented in Section 6.4, the analysis used interim data from the ongoing, open label Resistant Pathogen Study, D4280C00006, to provide additional supportive information for the clinical efficacy of CAZ-AVI against CAZ-NS pathogens. As stated above, there are concerns about exchangeability of subjects due to potential differences in doses and infusion time, baseline patient and disease characteristics, prognostic factors and the supportive care they had received.

Furthermore, in the meta-analyses described in Section 6.5, the Applicant submitted several studies that have used microbiological evaluable (ME), subsets of ME and a few studies with MITT as the analyses populations. There are considerable uncertainties in these studies and they are not similar with respect to design, dose, and duration of treatment, baseline disease characteristics, timing of assessment and other factors. However, our analysis only considered five studies, of which three used ME as the primary analysis population. Given the potential

uncertainties in the pooled meta-analyses findings such findings should only be considered as additional supportive evidence.

7. CLINICAL SAFETY

7.1. Clinical Trials Used to Assess Safety

The cumulative clinical safety database of avibactam and CAZ-AVI includes experience from Phase 1 and Phase 2 trials, as well as preliminary data from ongoing Phase 3 trials. In the completed Phase 1 and Phase 2 studies, 521 subjects have received CAZ-AVI (360 subjects) or avibactam alone (204). Of note, some of these subjects received both in cross-over studies. A total of 286 subjects have received either single or multiple doses of 2000/500 mg of CAZ-AVI (217 subjects) or 500 mg of avibactam alone (96 subjects). A summary of safety experience in completed Phase 1 and Phase 2 studies with avibactam alone and in combination with ceftazidime are shown in Table 38.

From the Phase 1 program, the majority of subjects received one to four days of study drug. Thirty-six subjects received CAZ-AVI or avibactam alone in multiple dose regimens for five to seven days and 24 subjects received 11 days of CAZ-AVI treatment. No subject received greater than 11 days of treatment.

Table 38: Completed Phase 1 and Phase 2 Studies with Avibactam Alone and in Combination with Ceftazidime

Study ID	*Phase*	*Study Type*	*AVI or CAZ-AVI n (rec. dose)*	*CAZ-AVI n (rec. dose)*	*AVI alone n (rec. dose)*
NXL104/1001	1	Single-dose escalation PK	56 (16)	16 (8)	56 (8)
NXL104/1002	1	Multiple-dose escalation PK	41 (24)	8 (8)	33 (16)
NXL104/1003	1	Single-dose PK avibactam, renal impairment	31 (0)	0	31 (0)
NXL104/1004	1	Single-dose PK avibactam, age and gender	33 (33)	0	33 (33)
D4280C00007	1	Thorough QT	46 (0)	46 (0)	0
D4280C00008	1	Distribution, metabolism and excretion	6 (6)	0	6 (6)
D4280C00009	1	ELF	43 (22)	43 (22)	0
D4280C00010	1	Single- and multiple-dose PK, Japanese subjects	13 (13)	7 (7)	6 (6)
D4280C00011	1	DDI PK, ceftazidime and avibactam	43 (43)	43 (43)	27 (27)
D4280C00012	1	DDI PK, metronidazole	28 (28)	28 (28)	0
CXL-PK-01	1	DDI PK, ceftaroline and avibactam	12 (0)	0	12 (0)
NXL104/2001	2	cUTI	68 (0)	68 (0)	0
NXL104/2002	2	cIAI	101 (101)	101 (101)	0
Total Subjects			**521 (286)**	**360 (217)**	**204 (96)**

rec. = recommended (i.e. 2000/500 mg of CAZ-AVI or 500 mg of avibactam alone)

Table 39: Ongoing Phase 1 and Phase 3 Studies

Study Number	**Number of Subjects[a]**		
	CAZ-AVI	**Comparator**	**Blinded**
Clinical Pharmacology Studies			
D4280C00014	24	—	—
D4280C00020	12	4	—
D4280C00023	13	—	—
Total Subjects: Phase 1	49	4	0
Phase 3 Trials			
D4281C00001 (HABP/VABP)	—	—	217
D4280C00001/5 (cIAI)	—	—	1057
D4280C00002/4 (cUTI)	—	—	903
D4280C00006 (cIAI and cUTI)	113	109	—
D4280C00018 (cIAI)	—	—	250
Total Subjects: Phase 3	113	109	2427
Total	**162**	**113**	**2427**

[a] Includes available exposure data as of 15 Jun 2014.

7.2. Overview of Adverse Events

In clinical trials with ceftazidime alone as described in the Fortaz® label, the most common adverse reactions were local intravenous site, allergic and gastrointestinal reactions. Fewer than 2% of patients experienced phlebitis, inflammation at the site of injection, diarrhea, nausea, vomiting and abdominal pain. Hypersensitivity reactions were reported in 2% of patients.[1]

Adverse reactions reported in post-marketing experience with ceftazidime include anaphylaxis, angioedema, urticaria, hyperbilirubinemia, and jaundice. Cephalosporin-class adverse reactions include colitis, toxic nephropathy, hepatic dysfunction (including cholestasis), aplastic anemia, hemorrhage. Toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have also been reported with cephalosporins, including ceftazidime. Abnormal laboratory tests include prolonged prothrombin time, false-positive test for urinary glucose, and pancytopenia. Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycosides or potent diuretics such as furosemide.

A review of the FDA Adverse Event Reporting System (FAERS) database and published literature regarding ceftazidime revealed no additional safety signals. However, while myoclonus and status epilepticus have been described, particularly in patients with renal failure, a specific subtype non-convulsive status epilepticus (NCSE) was reported in 18 of the 20 patients described in 14 publications. NCSE refers to a prolonged seizure diagnosed by electroencephalogram (EEG) that manifests primarily as altered consciousness or encephalopathy, as opposed to the dramatic convulsions seen in generalized tonic-clonic status epilepticus, and may occur even in the presence of dosing adjustments recommended for renally compromised patients.

In the cumulative CAZ-AVI clinical program, 61 deaths have been reported, including seven in the Phase 2 studies (4 CAZ-AVI, 3 comparator) and 54 in the ongoing Phase 3 studies (3 comparator, 3 CAZ-AVI and 48 remain treatment blinded). No deaths occurred in any completed Phase 1 study. In the ongoing Phase 1 studies, there have been no reported SAEs, discontinuations due to TEAEs, or deaths. In Trial 2001, there was one death reported in the comparator group. In Trial 2002, there were 6 deaths (4 CAZ-AVI, 2 meropenem), which are summarized in Table 40. Six deaths have been reported in the open-label Study D4280C00006 (3 CAZ-AVI, 3 BAT comparator). These deaths are summarized in Table 41. Based on the 12 narratives provided, each appears to be attributable to underlying comorbidities, treatment failure and/or emergent infection. Twenty-two deaths were reported in the Phase 3 cIAI trial (D4280C00001/5). Although this trial was recently completed, unblinded narratives are not yet available. No deaths have been reported in the ongoing Phase 3 cUTI trial (D4280C00002/4). Three deaths (1.2%) were reported in Study D4280C00018 (Asia cIAI) and 23 (10.6%) were reported in Study D4281C00001 (HABP/VABP). No deaths have been reported in the ongoing Phase 3 cUTI trial (D4280C00002/4). Three deaths (1.2%) were reported in Study D4280C00018 (Asia cIAI) and 23 (10.6%) were reported in Study D4281C00001 (HABP/VABP).

Table 40: Summary of TEAEs Associated with Deaths Reported during Trial 2002

ID	Treatment	AE Term	Day of AE	Day of Death	Comment
23004	Meropenem	Secondary peritonitis	5	36	82-year-old female with an intra-abdominal abscess; small bowel leakage occurred. Repeat surgery was performed; culture of lavage fluid grew *E. faecium*.
32001	CAZ-AVI + MTZ	Post-operative respiratory failure	1	67	54-year-old male with perforation of the sigmoid colon, multiple abdominal and pelvic abscesses. Discontinued from study by the investigator on Day 47 due to septic shock.
		Septic shock	1		
		Elevated ALT, AST, bilirubin	1		
42005	CAZ-AVI + MTZ	Multiple organ failure (renal, resp, neuro, cardiovasc)	7	13	72-year-old male with acute appendicitis and peri-appendiceal abscess. Deterioration due to pneumonia with pleural effusion.
63006	Meropenem	Hospital-acquired pneumonia	2	8	59-year-old male with ileal perforation and peritonitis. Sudden cardiorespiratory arrest on Day 8.
		Decrease in platelet count	4		
67001	CAZ-AVI + MTZ	Worsening of sepsis	10	20	40-year-old male with acute pancreatitis and intestinal perforation.
72003	CAZ-AVI + MTZ	Cardiac arrest	2	2	55-year-old male with perforated gastric ulcer and peritonitis, abdominal aneurysm and occluded bilateral femoral arteries, status post embolectomy.

Table 41: Summary of TEAEs Associated with Deaths Reported during Study D4280C00006

ID	Treatment	AE Term	Day of AE	Day of Death	Comment
E0205002	BAT	Acute respiratory failure	7	15	76-year-old female with severe aortic stenosis, chronic obstructive pulmonary disease, pericardial effusion with tamponade, status post pleuro-pericardial window.
E1801002	CAZ-AVI	Cardiorespiratory arrest	3	3	85-year-old female with cardiomyopathy, pulmonary tuberculosis, recurrent UTI, renal insufficiency.
E1803001	CAZ-AVI	Cardiorespiratory arrest, pulmonary thromboembolism	17	17	85-year-old female with left hip fracture, status post arthroplasty, UTI
E4002001	Meropenem	Respiratory failure due to pneumonia	2	6	66-year-old male status post lung transplantation for emphysema, diverticulosis, perforation of small bowel, ileal conduit, metastatic transitional cell carcinoma treated for gangrenous rupture of the gallbladder, developed lobar pneumonia.
E4002002	Meropenem	Cardio-respiratory arrest	18	18	78-year-old female status post cerebral vascular event, normal pressure hydrocephalus with shunt, chronic renal failure. Cardiac arrest after discharge at nursing home.
E7002002	CAZ-AVI	Renal failure, congestive heart failure	14	22	85-year-old female with chronic renal and heart failure. Concomitant diuretics, worsening azotemia, hyperkalemia. Family: palliative care.

Nearly all of the subjects in the Phase 1 safety population completed their study, including 99% of all subjects receiving avibactam alone and 97.7% of subjects in the CAZ-AVI and CAZ-AVI + MTZ groups combined. In healthy volunteers receiving avibactam alone, 98.8% completed study drug, as did 98.6% of subjects receiving either other comparators (moxifloxacin or metronidazole) or placebo. One subject, a 21 year-old black male in Study D4280C00007 (E0001082) who was receiving a high dose of CAZ-AVI (3 g ceftazidime plus 2 g avibactam), was discontinued due to a TEAE during infusion. The investigator reported the AE as urticaria of mild severity occurring 37 minutes after the start of the infusion on Day 5. The subject was given one dose of 50 mg IV diphenhydramine and the event completely resolved in 1.6 hours.

In Trial 2001, 18 subjects (26.5%) in the CAZ-AVI group prematurely discontinued the study compared to 11 (16.4%) in the comparator group. Two (2.9%) of the discontinuations were associated with non-fatal SAEs (accidental overdose and atrial fibrillation) in the CAZ-AVI group. There were no TEAEs resulting in discontinuation in the comparator group. In Trial 2002, 8 subjects (7.9%) in the CAZ-AVI group prematurely discontinued the study compared to 7 (6.9%) in the comparator group. Two SAEs in one subject (pruritic rash and hepatic enzyme increased in Subject 52005 who received CAZ-AVI + MTZ) contributed to premature discontinuation of study drug. Another subject (63007) in the CAZ-AVI + MTZ group discontinued therapy during the third dose of study drug due to a non-serious TEAE (generalized rash). A total of 5 (5.0%) subjects had TEAEs resulting in discontinuation of study drug in the CAZ-AVI + MTZ group, and 3 (2.9%) in the meropenem group.

As of 25 June 2014 in the ongoing blinded Phase 3 studies, 228 SAEs were reported in 180 (6.8%) subjects, and 46 subjects discontinued study drug due to an AE. In Study D4280C00006, 8 serious adverse events (SAEs) were reported in 8 of the 113 subjects treated with CAZ-AVI, and 8 SAEs were reported in 7 of the 109 subjects treated with a comparator. The most common TEAE resulting in premature discontinuation across all ongoing Phase 3 studies was drug eruption, occurring in 3 subjects across all Phase 3 studies. Treatment group assignments in these studies remain blinded. In Study D4280C00006, 3 subjects discontinued study drug due to a TEAE (1 CAZ-AVI, 2 comparator). The subject in the CAZ-AVI group was noted to have discontinued study drug due to cardio-respiratory arrest which was also a fatal SAE. For the two subjects in the BAT comparator group, one subject had lobar pneumonia and the other had *C. difficile*-associated diarrhea (CDAD).

There were no cases of CDAD in the completed CAZ-AVI Phase 1 studies and Phase 2 trials. CDAD was reported in 3 subjects in the ongoing blinded Phase 3 trials. Hypersensitivity reactions were also considered to be of special interest. No TEAEs representing hypersensitivity/anaphylaxis resulted in death during any Phase 1 study or Phase 2 trial. In the ongoing blinded Study D4280C00005, two cases (hypersensitivity and drug eruption) were reported as treatment-emergent SAEs.

Table 42 and Table 43 list non-fatal SAEs in Trial 2001 and Trial 2002, respectively. SAEs (fatal and non-fatal) were reported in 8.8% and 3.0% in the cUTI trial and 8.9% and 10.8% in the cIAI trial and for CAZ-AVI (± MTZ) and comparators, respectively. No SAE occurred in more than two

subjects in either treatment group. The most common SAEs were in the Gastrointestinal Disorders and Infections and Infestations system organ classification.

Table 42: Trial 2001 –Subjects with Non-Fatal Serious Adverse Events

AE Term	CAZ-AVI 500mg/125mg IV q 8hr		IMI-CS 500mg IV q6h		Total	
	N=68		N=67		N=135	
	n	%	n	%	n	%
Atrial Fibrillation	1	1.5	0	0.0	1	0.7
Diarrhea	1	1.5	0	0.0	1	0.7
Pyelonephritis	1	1.5	0	0.0	1	0.7
Accidental Overdose	1	1.5	0	0.0	1	0.7
Intervertebral Disc Protrusion	1	1.5	0	0.0	1	0.7
Renal Failure Acute	1	1.5	0	0.0	1	0.7
Renal Impairment	1	1.5	0	0.0	1	0.7
Renal Abscess	0	0.0	1	1.5	1	0.7
Urosepsis	0	0.0	1	1.5	1	0.7
Blood Creatinine Increased	0	0.0	1	1.5	1	0.7

Table 43: Trial 2002 – Number of Subjects with Nonfatal Serious Adverse Events

AE Term	CAZ-AVI 2000mg/500mg IV q8h + MTZ 500mg IV q8h		MER 1000mg IV q 8hr + placebo MTZ IV q8h		Total	
	N=101		N=102		N=203	
	n	%	n	%	n	%
Cardiac Arrest	1	1.0	0	0.0	1	0.5
Intestinal Obstruction	1	1.0	2	2.0	3	1.5
Gastric Perforation	1	1.0	0	0.0	1	0.5
Localized Intraabd Fluid Collection	1	1.0	0	0.0	1	0.5
Volvulus	1	1.0	0	0.0	1	0.5
Multi-Organ Failure	1	1.0	0	0.0	1	0.5
Pneumonia	1	1.0	1	1.0	2	1.0
Postoperative Abscess	1	1.0	1	1.0	2	1.0
Sepsis	1	1.0	0	0.0	1	0.5
Septic Shock	1	1.0	0	0.0	1	0.5
Hepatic Enzyme Increased	1	1.0	0	0.0	1	0.5
Respiratory Distress	1	1.0	0	0.0	1	0.5
Atrial Fibrillation	0	0.0	1	1.0	1	0.5
Peritonitis	0	0.0	1	1.0	1	0.5
Wound Secretion	0	0.0	1	1.0	1	0.5
Platelet Count Decreased	0	0.0	1	1.0	1	0.5
Diabetes Mellitus	0	0.0	1	1.0	1	0.5
Renal Failure Acute	0	0.0	1	1.0	1	0.5
Respiratory Disorder	0	0.0	1	1.0	1	0.5
Tracheo-esophageal Fistula	0	0.0	1	1.0	1	0.5

Table 44 and Table 45 list the most common TEAE's occurring in greater than 5% of subjects sorted by decreasing incidence in the CAZ-AVI-(±MTZ)-treated group for Trials 2001 and 2002, respectively.

Table 44: Trial 2001 - Subjects Experiencing at Least One Adverse Event in Greater Than 5% of CAZ-AVI Subjects

AE Term	CAZ-AVI 500mg/125mg IV q 8hr		IMI-CS 500mg IV q6h		Total	
	N=68		N=67		N=135	
	n	%	n	%	n	%
Headache	14	20.6	21	31.3	35	25.9
Constipation	7	10.3	2	3.0	9	6.7
Anxiety	7	10.3	5	7.5	12	8.9
Diarrhea	6	8.8	7	10.4	13	9.6
Abdominal Pain	6	8.8	3	4.5	9	6.7
Abdominal Pain Upper	5	7.4	1	1.5	6	4.4
Chest Pain	4	5.9	3	4.5	7	5.2
Hyperglycemia	4	5.9	3	4.5	7	5.2
Dizziness	4	5.9	0	0.0	4	3.0
Insomnia	4	5.9	4	6.0	8	5.9
Hypertension	4	5.9	2	3.0	6	4.4

Table 45: Trial 2002 - Subjects Experiencing at Least One Adverse Event in Greater Than 5% of CAZ-AVI Subjects

AE Term	CAZ-AVI 2000mg/500mg IV q8h + MTZ 500mg IV q8h		MER 1000mg IV q 8hr + placebo MTZ IV q8h		Total	
	N=101		N=102		N=203	
	n	%	n	%	n	%
Vomiting	14	13.9	5	4.9	19	9.4
Nausea	10	9.9	6	5.9	16	7.9
Blood alk phos increased	10	9.9	7	6.9	17	8.4
Pyrexia	9	8.9	11	10.8	20	9.9
AST increased	9	8.9	16	15.7	25	12.3
ALT increased	8	7.9	14	13.7	22	10.8
Abdominal pain	7	6.9	4	3.9	11	5.4
Pyuria	6	5.9	5	4.9	11	5.4
Cough	6	5.9	4	3.9	10	4.9
Diarrhea	5	5.0	5	4.9	10	4.9
WBC count increased	5	5.0	6	5.9	11	5.4
Anxiety	5	5.0	1	1.0	6	3.0
Hematuria	5	5.0	6	5.9	11	5.4

Table 46 and Table 47 also summarize the most common TEAEs, for Trials 2001 and 2002, respectively; however, AEs are sorted by risk difference. Since this is an exploratory analysis with low incidence of events, confidence intervals and P-values are not reported.

Table 46: Trial 2001: Adverse Events with Risk Difference Greater Than 2 (per 100)

AE Term	CAZ-AVI 500mg/125mg IV q 8hr		IMI-CS 500mg IV q6h		RD (per 100)
	n	%	n	%	
Constipation	7	10.3	2	3.0	7.3
Dizziness	4	5.9	0	0.0	5.9
Abdominal pain upper	5	7.4	1	1.5	5.9
Diabetes mellitus	3	4.4	0	0.0	4.4
Fungus urine test positive	3	4.4	0	0.0	4.4
Abdominal pain	6	8.8	3	4.5	4.4
Anorexia	2	2.9	0	0.0	2.9
Chest discomfort	2	2.9	0	0.0	2.9
Rhinorrhea	2	2.9	0	0.0	2.9
Vaginal candidiasis	3	4.4	1	1.5	2.9
Hypertension	4	5.9	2	3.0	2.9
Anxiety	7	10.3	5	7.5	2.8

Table 47: Trial 2002: Adverse Events with Risk Difference Greater Than 2 (per 100)

AE Term	CAZ-AVI 2000mg/500mg IV q8h + MTZ 500mg IV q8h		MER 1000mg IV q 8hr + placebo MTZ IV q8h		RD (per 100)
	n	%	n	%	
Vomiting	14	13.9	5	4.9	9.0
Nausea	10	9.9	6	5.9	4.0
Anxiety	5	5.0	1	1.0	4.0
Hypokalemia	4	4.0	0	0.0	4.0
Blood alk phos increased	10	9.9	7	6.9	3.0
Abdominal pain	7	6.9	4	3.9	3.0
Constipation	4	4.0	1	1.0	3.0
Tachycardia	4	4.0	1	1.0	3.0
Pain	3	3.0	0	0.0	3.0
Urinary tract infection	3	3.0	0	0.0	3.0
Cough	6	5.9	4	3.9	2.0

7.3. LABORATORY FINDINGS

Transient elevations in one or more of the hepatic enzymes, including aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT) and alkaline phosphatase (ALP), have been reported with ceftazidime. TEAEs and potentially clinically significant post-baseline chemistry values representing liver disorders were low, consistent with ceftazidime and cephalosporin class, and similar between the CAZ-AVI and comparator groups. No cases meeting Hy's Law criteria (3-fold or greater AST or ALT elevation above the upper-limit of normal plus an elevation of total bilirubin greater than twice the upper-limit of normal without initial cholestasis, elevated ALP or other alternative explanation for ongoing liver injury) have been reported in any CAZ-AVI-treated subject in any study to date.

Post-baseline creatinine elevations were rare in the Phase 2 studies, and reveal a similar profile to the compactors and ceftazidime alone. Other adverse events of special interest include hematologic and coagulation disorders. CAZ-AVI had no observable effect on hematologic or coagulation parameters above that of the comparators studied.

7.4. Other Safety Explorations

For the analysis of QT/QTc prolongation from Study D4280C00007, the least squares mean and two-sided 90% CI for CAZ-AVI compared to placebo for the change from baseline in QTcF was estimated at each of the 10 post-dose time points. PK parameters for ceftazidime and avibactam confirmed supratherapeutic exposures at the doses administered. In the primary comparison of QTcF of avibactam 2000 mg/ceftazidime 3000 mg versus placebo, the upper bound of the 2-sided 90% CI did not exceed 10 msec at any time point post-dose. In addition, there were no QTcF intervals greater than 450 msec nor were there any QTcF interval changes from baseline greater than 30 msec after a single IV dose of avibactam 2000 mg/ceftazidime 3000 mg.

Table 48: Study D4280C00007: Largest Least-Squares Mean Difference from Placebo in Time-Matched QTcF for CAZ-AVI and Moxifloxacin—Pharmacodynamic Analysis Set

Parameter	**CAZ-AVI N = 44**	**Moxifloxacin N = 45**
Largest least squares mean difference estimate from time-matched placebo (ΔΔQTcF), msec	4.1	9.8
Time of largest difference	1 hour	3 hours
90% CI for the largest least squares mean difference, msec	2.3, 5.9	8.0, 11.6

CI = confidence interval; ΔΔQTcF = placebo-corrected change from baseline in QTcF.

In Trials 2001 and 2002, electrocardiograms were recorded as a bedside safety parameter. Mean post-baseline QTcF average changes for the CAZ-AVI (± MTZ) and comparator groups and mean post-baseline changes at End of IV Therapy were small and similar. Two subjects (one in the CAZ-AVI group in Trial 2001 and one in the meropenem group in Trial 2002) had QTcF values > 500 msec and changes from baseline > 60 msec based on the centrally read ECG values. Neither subject had associated cardiac TEAEs reported. The incidences of subjects with prolongation of QTc intervals in the Phase 2 are summarized in Table 49.

Table 49: Summary of QTcF in the Phase 2 Studies—Safety Population

QTcF ECG Parameter	Trial 2001		Trial 2002	
	CAZ-AVI (N = 40)	Imipenem (N = 46)	CAZ-AVI + MTZ (N = 68)	Meropenem (N = 66)
Post-baseline Average Change at End of IV Therapy				
N1	40	45	63	61
Mean	14.9	5.1	9.3	8.1
Min, Max	-46, 105	-35, 65	-61, 80	-74, 236
Post-baseline Value at End of IV Therapy, n/N1 (%)				
> 450 to ≤ 480 msec	1/40 (2.5)	2/45 (4.4)	5/63 (7.9)	0/61
> 480 to ≤ 500 msec	0/40	0/45	0/63	1/61 (1.6)
> 500 msec	1/40 (2.5)	0/45	0/63	1/61 (1.6)
Post-baseline Change at End of IV Therapy, n/N1 (%)				
> 30 to ≤ 60 msec	6/40 (15.0)	4/45 (8.9)	7/63 (11.1)	10/61 (16.4)
> 60 msec	4/40 (10.0)	2/45 (4.4)	2/63 (3.2)	2/61 (3.3)

N1 = number of subjects with a baseline and post-baseline value

8. POINTS FOR ADVISORY COMMITTEE DISCUSSION

1. Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime/avibactam for the proposed indication of complicated intra-abdominal infections, when limited or no alternative treatments are available?
   - If yes, please provide any recommendations concerning labeling.
   - If no, what additional studies/analyses are needed?

2. Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime/avibactam for the proposed indication of complicated urinary tract infections, including pyelonephritis, when limited or no alternative treatments are available?
   - If yes, please provide any recommendations concerning labeling.
   - If no, what additional studies/analyses are needed?

3. Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime/avibactam for the proposed indication of aerobic gram-negative infections (including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia) with limited treatment options?
   - If yes, please provide any recommendations concerning labeling.
   - If no, what additional studies/analyses are needed?

9. APPENDIX

Table 50: Studies Used to Estimate the Treatment Effect of Ceftazidime Alone in Adult Patients with cUTI

Citation	Study design	Ceftazidime Dosage	Clinical Assessment Time Point	Favorable Clinical Response		Microbiological Assessment Time Point	Favorable Microbiological Response		Analysis Population
				Ceftazidime	Comparator		Ceftazidime	Comparator	
Cox, 1983	Randomized	0.5 g IM q12h, 5-10 days	Follow-up	31/33	26/29	5-9 days post treatment	30/33	25/29	Possibly MITT
Cox, 1991	Randomized	1 g IV q12h for ≥3 days, then oral switch option	1 week following therapy	30/30	36/38	5-9 days after discontinuation of therapy	30/30	37/38	MITT
Cox, 1993	Randomized, open label	0.5-2 g IV TID or 1-2 g IV BID, 4-21 days	5-9 days post treatment	73/82	142/165	5-9 days post treatment	78/82	155/165	ME
Frimodt-Moller and Masen, 1983		0.5 g IM q12h, 7-10 days	N/A	N/A	N/A	5-9 days after treatment	16/22	13/21	
Gallis et al, 1989	Randomized, blinded	0.5 g q8-12h, 7-14 days	N/A	N/A	N/A	5-9 days after completion of therapy	0/1 (cUTI)	4/4	Subset of ME
Holloway and Palmer, 1996	Randomized, open label	2 g IV or IM q8h	1 week after end of therapy	38/48	42/48	After treatment	43/48	42/48	Subset of ME
Horowitz et al, 1985	Randomized, open label	0.5 g IV q12h	N/A	N/A	N/A	5-9 days post therapy	20/27	14/27	ME
Melekos et al, 1991	Randomized, open label	1 g IV or IM BID, 7 days	5-9 days post treatment	18/22	16/19 (aztreonam) 17/20 (amikacin)	5-9 days post treatment	12/12	5/9	ME
Mouton and Beuscart, 1995	Randomized, open label	2 g q8h IV	N/A	N/A	N/A	5-9 days post treatment	12/12	5/9	Subset of ME
Romanelli and Cravarezza, 1995	Randomized, open label	0.5 g TID IM, 5-10 days	N/A	N/A	N/A	5-9 days post treatment	11/15	17/28	Subset of ME
Schalkhauser and Kohler, 1992	Randomized, open label	1 g IV BID, 7-10 days	3-5 days post treatment	76/78	83/85	3-5 days post treatment	69/78	74/85	ME
Sharifi et al, 1996	Randomized, open label	0.5 g q12h IM or IV, ≤ 14 days	5-9 days post treatment	43/50	83/93	5-9 days post treatment	39/50	83/98	Subset of ME
Sifuentes-Osornio et al, 1989	Randomized, blinded	1 g q8h IV 7-14 days	N/A	N/A	N/A	Day 3 or 4 and 5-9 days post treatment	8/9	14/16	Subset of ME
Study Group, 1992	Randomized, open label	1 g IV q12h, ≥5 days	N/A	N/A	N/A	2-15 days post treatment	174/200	337/377	ME
Tammela et al, 1990	Randomized	2 g BID IV for 3-4 days then mostly IM, 5-15 days	Days 5-9 of follow-up	31/38	29/39	Days 5-9 of follow-up	30/38	28/39	ME

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