CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206494Orig1s000

MEDICAL REVIEW(S)

Memo to File

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Memo
NDA #	206494
Applicant Name	Cerexa Inc.
Date of Submission	June 25, 2014
PDUFA Goal Date	February 25, 2015
Established (USAN) Name	Ceftazidime-avibactam
Trade Name	AVYCAZ
Dosage Forms / Strength	Injection/2 grams ceftazidime and 0.5 grams avibactam in single use vials
Indications	1. Complicated urinary tract infections (cUTI), including pyelonephritis for patients who have limited or no alternative treatment options 2. Complicated intra-abdominal infections (cIAI), used in combination with metronidazole for patients who have limited or no alternative treatment options

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Cross-Discipline Team Leader Review	Hala Shamsuddin MD
Pharmacology Toxicology Review	Armand Balboni MD PhD JD Wendelyn Schmidt PhD
Chemistry Manufacturing and Controls Review	Zhengfang Ge PhD
Medical Officer Review	Benjamin Lorenz MD
Statistical Review	Margaret Gamalo PhD
Risk Management	Joyce Weaver Pharm D
Product Quality Review	Robert Mello PhD
Microbiology Review	Avery Goodwin PhD
Clinical Pharmacology Review	Seong Jang PhD
Office of Scientific Investigations	Janice Pohlman MD MPH
Division of Medication Error Prevention and Analysis	Sevan Kolejian Pharm D Justine Harris RPh
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D

NDA 206494, Ceftazidime-avibactam was submitted by Cerexa Inc. on June 25, 2014. The Applicant proposed the following indications:

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

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

3. Aerobic Gram-negative infections with limited treatment options: ceftazidime-avibactam may be used for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP), and bacteremia where limited or no alternative therapies are available and the infection is caused by *E. coli, K. pneumoniae, K. oxytoca, P. aeruginosa, P. stutzeri, P. stuartii, C. freundii, C. koseri, Serratia spp., E. aerogenes, E. cloacae,* and *Proteus spp.,* including *P. mirabilis* and indole-positive *Proteus*. (b) (4)

Since submission of the NDA, the Applicant clarified that they were seeking all the above indications when limited or no alternative treatments are available.

All primary reviews and the CDTL review have been completed. However, a final recommendation regarding the acceptability of the facilities is not yet available. Although, the CMC review concluded that the information provided was generally satisfactory to assure the identity, strength, purity, and quality of the drug substances and the drug product, because of the outstanding inspections of the manufacturing and testing facilities at the time the review was required to be completed [under the requirements of the Program (PDUFA V applications], Dr. Ge did not recommend approval of the NDA.

I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of ceftazidime-avibactam for the treatment of adults with complicated

urinary tract infections and complicated intra-abdominal infections when limited or no alternative treatment options are available. I also agree with the review team that adequate data have not been provided to support approval for the Limited Use indication of treatment of aerobic gram-negative infections, including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia and bacteremia, where limited or no alternative therapies are available. However, I am unable to make a final recommendation on the regulatory action for this NDA as the status of the facilities is still under review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUMATHI NAMBIAR
02/18/2015

CLINICAL REVIEW

Application Type	505(b)(2) Type 1 NME, Type 4 New Combination
Application Number(s)	206494
Priority or Standard	Priority
Submit Date(s)	25 June 2014
Received Date(s)	25 June 2014
PDUFA Goal Date	25 February 2015
Division / Office	DAIP / OAP
Reviewer Name(s)	Benjamin Lorenz, MD
Review Completion Date	12 February 2015
Established Name	Ceftazidime-avibactam
Proposed Trade Name(s)	Cazavi, Avycaz
Therapeutic Class	Cephalosprin + β-lactamase inhibitor
Applicant	Cerexa, Inc (subsidiary of Forest Laboratories, Inc.)
Formulation(s)	Intravenous
Dosing Regimen	2.5 g (2 g ceftazidime + 0.5 g avibactam) IV q8h
Indication(s)	Complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), including acute pyelonephritis (AP), and aerobic Gram-negative infections with limited treatment options
Intended Population(s)	Adults

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the review of clinical safety and efficacy, there is adequate evidence to recommend approval of ceftazidime-avibactam (CAZ-AVI) for the treatment of adults with complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) when limited or no alternative treatment options are available. There is insufficient experience from human clinical trials at this time, however, to support approval for the following "Limited Use" indication: treatment of aerobic gram-negative infections, including hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) and bacteremia when limited or no alternative therapies are available.

1.2 Risk Benefit Assessment

As a 505(b)(2) application, evaluation of efficacy and safety relies on previous findings for ceftazidime as described in the FORTAZ® label and historical data for ceftazidime as described in published literature. Avibactam is a new chemical entity (NCE) that demonstrates a contributory effect only when given in combination with a β-lactam (such as ceftazidime) for the treatment of certain β-lactamase-producing pathogens. Support for the contribution of the avibactam in the combination with ceftazidime was drawn from non-clinical studies, including in vitro microbiology, animal models, and from clinical data, particularly for subjects with infections due to ceftazidime-non-sensitive (CAZ-NS) pathogens. In animal models, such as pyelonephritis and systemic infection established by intraperitoneal injection in mice, CAZ-AVI demonstrated activity (improved survival and decreased bacterial load) for infections caused by Class A and Class C serine β-lactamase-producing bacteria, against which ceftazidime alone was ineffective.

The Applicant submitted results of two Phase 2 trials, one each in cUTI (NXL104/2001, or Trial 2001) and cIAI (NXL104/2002, or Trial 2002). Interim data are also available for a limited number of subjects with cUTI and cIAI caused by CAZ-NS pathogens from an ongoing open-label Resistant Pathogen study (D4280C00006). Although a Phase 1 study showed that CAZ-AVI penetrates the epithelial lining fluid, and while a Phase 3 HABP/VABP trial is ongoing, there is currently no clinical trial data available to be able to assess the benefit of CAZ-AVI for the treatment of HABP/VABP or bacteremia. Neither of the two Phase 2 trials were designed with formal pre-specified hypotheses or powered for any statistical inference testing (statistical analyses are based only on descriptive data summaries), but the results provided important conclusions leading to the proposed recommended doses.

Trial 2001 studied CAZ-AVI with 500 mg ceftazidime + 125 mg avibactam, a dose that was 25% of the dose currently proposed for the treatment of cUTI. The most informative clinical

observations demonstrating the added benefit of avibactam were based on a limited number of subjects with infections caused by CAZ-NS pathogens. Among treated subjects who had an adequate baseline culture (mMITT population), 63.0% (29/46) in the CAZ-AVI group achieved both clinical cure and microbiologic eradication at the Test of Cure (TOC) visit compared to 51.0% (25/49) of subjects treated with imipenem-cilastatin. In the subgroup with a CAZ-NS pathogen, 57.1% (8/14) of CAZ-AVI treated subjects achieved both clinical cure and microbiologic eradication compared to 38.9% (7/18) in the imipenem group. All CAZ-NS pathogens in the CAZ-AVI group were *Escherichia coli*.

Trial 2002 studied the 2.5 gram dose of CAZ-AVI (2 g ceftazidime + 0.5 g avibactam) using a 30 minute infusion. In the mMITT population, a favorable clinical response was achieved in 82.4% (70/85) of subjects treated with CAZ-AVI + metronidazole versus 88.8% (79/89) treated with meropenem. In the subgroup of subjects with infections caused by CAZ-NS pathogens, clinical response was 90.0% (27/30) in the CAZ-AVI group and 82.6% (19/23) in the meropenem group. The most common CAZ-NS pathogens in the CAZ-AVI group were *E. coli* and *Klebsiella pneumoniae*. Based on pharmacokinetic analysis of systemic exposure and joint target attainment for pathogens with higher MICs, the proposed regimen for both cUTI and cIAI includes the recommendation for infusions to be given over 2 hours rather than 30 minutes.

Interim data from the ongoing Resistant Pathogen Study (using the final proposed dose of 2.5 grams IV infused over 2 hrs q8h for both cUTI and cIAI caused by CAZ-NS pathogens) included 4 subjects with cIAI and 44 subjects with cUTI. Nineteen of 21 subjects (90.5%) with cUTI were clinical cures compared to 18 of 23 (78.3%) subjects with best-available therapy (BAT). One patient with cIAI was treated with CAZ-AVI and was a clinical cure, whereas 1 of 3 subjects treated with BAT was a clinical cure at TOC.

Two Phase 3 trials, one each in cUTI and cIAI, were recently completed; however, only preliminary results from the cIAI trial (the RECLAIM trial) were available for this review. Despite pharmacokinetic (PK) modeling to support the initially proposed dose for patients with renal impairment (Trials 2001 and 2002 excluded subjects with CrCL < 70 and <50 mg/mL, respectively), preliminary subgroup analyses from the RECLAIM trial of subjects with a creatinine clearance (CrCL) between 30 and 50 mg/mL showed a decrease in clinical cure rates (14/31, 45%) versus meropenem (26/35, 74%) and an imbalance in mortality (8 deaths [25.8%] in the CAZ-AVI group compared to 3 deaths [8.6%] in the meropenem group). Although these results will require further review as more data become available, the CAZ-AVI label can inform prescribers regarding the need to follow CrCL daily for patients with baseline renal impairment and adjust the dose accordingly, particularly in the setting of changing renal function. Because the percentage of time that free-drug concentrations are above the minimum inhibitory concentration (%*f*T > MIC) is the most relevant PK/PD index for ceftazidime, and the Fortaz label recommends an increase in the total daily ceftazidime dose of 50% (to no more than 6 grams) for patients with severe infections and require dose adjustment, an increase in frequency to the initially proposed renal dosing adjustments is recommended.

The imbalance in outcomes among subjects with baseline renal impairment is the most concerning safety issue. Whether this is more likely to have been related to a chance finding or inadequate ceftazidime dose is uncertain. A specific toxicity associated with addition of avibactam, however, is less likely. Overall, CAZ-AVI demonstrated a favorable safety profile, and the adverse reactions observed were comparable to ceftazidime alone and other comparators, such as meropenem. When considered for treatment of cUTI and cIAI, particularly those caused by CAZ-AVI-susceptible pathogens where alternative treatment options are limited, and when used in accordance with the recommended labeling, the benefit of CAZ-AVI outweighs the potential risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Division of Risk Management in the Office of Medication Error Prevention and Management reviewed the application and determined that a Postmarket Risk and Evaluation Strategy (REMS) for the management of the risks associated with CAZ-AVI was not recommended. This reviewer agrees that there is adequate safety information to recommend routine pharmacovigilance as a sufficient strategy for postmarket risk evaluation.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant submitted a deferral request with their initial pediatric study plan, which assumes that efficacy can be extrapolated from adult data for cIAI and cUTI in pediatric patients as young as 3 months of age. Pursuant to PREA requirements, an open-label single-dose trial to evaluate the pharmacokinetic, safety and tolerability of CAZ-AVI in children 3 months to less than 18 years with a suspected or confirmed bacterial infection and receiving other systemic antibacterial therapy was recently completed. Pending determination of appropriate doses for each age group, a multiple-dose, active-controlled trial will be recommended to evaluate safety, tolerability and efficacy of CAZ-AVI in children with cUTI and cIAI from 3 months to less than 18 years of age. An additional PK and safety study to include neonates from birth to 3 months will be recommended as well.

After the initial NDA submission, preliminary results from the Phase 3 cIAI trial showed a mortality imbalance and decreased efficacy in the subgroup of subjects with baseline moderate to severe renal impairment. Although the Applicant's proposed adjustments in response to these findings appear to be adequate (based on PK/PD modeling) and may potentially address the imbalance in this patient population, the relationship between drug exposure and treatment response and the adequacy of these adjustments have not yet been clearly established. The following PMR is therefore recommended: Conduct a trial or submit other data from the Phase 3 trial in cIAI to evaluate the PK, safety, efficacy, and PK and safety and clinical outcomes in adult patients with baseline renal impairment (creatinine clearance of 50 mL/min or less) receiving of AVYCAZ (ceftazidime-avibactam) dosing regimens.

After the introduction of CAZ-AVI to the market, a five-year study to determine if decreased susceptibility is occurring in the target population of bacteria will also be recommended.

2 Introduction and Regulatory Background

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.

Relying on the FDA's previous findings of efficacy and safety of ceftazidime, as well as published literature on ceftazidime, the Applicant has submitted this NDA for CAZ-AVI through the 505(b)(2) pathway. 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 cIAI and 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 HABP/VABP is ongoing. Phase 3 trials in cUTI and cIAI were recently completed.

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 bacteremia where 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*.

2.1 Product Information

Ceftazidime was initially approved in 1985 under the trade name FORTAZ® (in 2011 Covis Pharma acquired the U.S. Rights from GlaxoSmithKline for Fortaz, the RLD for ceftazidime). The currently approved indications in the ceftazidime label include: lower respiratory tract infections, skin and skin structure infections, urinary tract infections, bacterial septicemia, bone and joint infections, gynecologic infections, intra-abdominal infections, and central nervous system infections. Ceftazidime has been a well-established treatment of certain bacterial infections caused by susceptible pathogens, including complicated urinary tract infections (cUTI) caused by *Pseudomonas aeruginosa*, *Enterobacter* spp., *Proteus* spp., *Klebsiella* spp., and *Escherichia coli,* and serious intra-abdominal infections (cIAI), including peritonitis caused by *E. coli*, *Klebsiella* spp., *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms.

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.[1,2] 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 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. Concurrent administration of metronidazole is recommended when anaerobic infection is suspected (e.g., for cIAI). Patients with renal impairment should have the dosage of CAZ-AVI modified according to the estimated measured creatinine clearance (CrCL), shown as follows in Table 1.

Medical Officer comment: Based on preliminary results from the Phase 3 cIAI trial that were submitted to the NDA mid-cycle, dose recommendations for patients with renal impairment have been amended. Please refer to Table 98 and additional discussion in Section 7.7.

Table 1: Proposed Dosage of CAZ-AVI in Patients with Renal Impairment

Estimated CrCL (mL/min)[a]	Recommended Dosage Regimen for CAZ-AVI
> 50	2.5 g (2 g ceftazidime + 0.5 g avibactam) infused every 8 hours over 2 hours
31 to ≤ 50	1.25 g (1 g ceftazidime + 0.25 g avibactam) infused every (b) (4) hours over 2 hours
16 to ≤ 30	(b) (4) g ceftazidime + 0 (b) (4) g avibactam) infused every 24 hours over 2 hours
6 to ≤ 15	(b) (4) g ((b) (4) ceftazidime + (b) (4) g avibactam) infused every 24 hours[b] over 2 hours
≤ 5	(b) (4) g ((b) (4) g ceftazidime + (b) (4) g avibactam) infused every 48 hours[b] over 2 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.

The infusion time for CAZ-AVI in the ongoing Phase 3 program and the proposed labeled dosing regimen was increased compared to the Phase 2 studies based on the probability of PK/PD target attainment (PTA) simulations, which found that while a 2 g ceftazidime + 0.5 g avibactam dose is optimal and that the 30-minute infusion may not achieve adequate probability of joint PK/PD target attainment for organisms with higher minimum inhibitory concentrations (MICs). The simulations demonstrated that this would be better achieved by a 2-hour infusion.

The drug product is white to yellow powder in 20 mL (nominal capacity), sterile vials. The qualitative and quantitative composition of the drug product is presented in Table 2.

Table 2: Composition of the Drug Product

Components	Function	Standard	Quantity (per unit)
Avibactam sodium[a]	Drug substance	In-house	(b) (4) mg[b]
Ceftazidime pentahydrate/sodium carbonate[c]	Drug substance	USP/NF	2635 (b) (4) mg[b]
Total vial fill weight			(b) (4) mg

[a] Equivalent to (b) (4) mg of avibactam free acid, weight adjusted for purity. Nominal strength of 500 mg avibactam.
[b] Quantity includes a (b) (4) % overfill, applied to account for the extractable volume from the reconstituted vial.
[c] Equivalent to (b) (4) mg of ceftazidime pentahydrate (equivalent to (b) (4) mg of ceftazidime) and 239.6 mg sodium carbonate as a blend. Ceftazidime weight adjusted for purity. Nominal strength of 2000 mg ceftazidime.

The vial presentation is designed for single dose use. Upon reconstitution in the vial, the dose is then further diluted with a suitable infusion fluid prior to administration by intravenous infusion.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 3: Currently Available Treatments for cIAI by Antibacterial Class

Generic name	Trade name	Comments
Extended-spectrum penicillins		
Piperacillin	Pipracil	
Cephalosporins (parenteral 2nd, 3rd and 4th generation)		Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli
Cefotetan	Cefotan	
Cefoxitin	Mefoxin	
Cefotaxime	Claforan	
Ceftazidime	Fortaz, Tazicef	
Ceftriaxone	Rocephin	
Cefepime	Maxipime	
β-lactam/β-lactamase Inhibitor Combinations		
Ticarcillin clavulanate	Timentin	
Ampicillin-sulbactam	Unasyn	
Piperacillin-tazobactam	Zosyn	
Ceftolozane-tazobactam	Zerbaxa	
Fluoroquinolones		Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy
Ciprofloxacin	Cipro	
Moxifloxacin	Avelox	
Carbapenems		
Imipenem-cilastatin	Primaxin	
Meropenem	Merrem	
Ertapenem	Envanz	
Doripenem	Doribax	
Monobactams		Addition of an agent against gram-positive cocci is recommended. Although used in pts with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime
Aztreonam	Azactam	
Aminoglycosides		
Gentamicin		
Amikacin		
Tobramycin		
Glycylcyclines		Vancomycin-resistant *Enterococcus faecium* (VREF) activity, but *Pseudomonas aeruginosa* is intrinsically resistant to tigecycline
Tigecycline	Tygacil	
Polymyxins		Safety risks including nephrotoxicity and rare but serious neurotoxicity; Lack of supportive data to guide dosing; Some gram-negatives are intrinsically resistant (e.g. *Proteus* spp. *Providencia* spp. *Serratia* spp., *B. cepacia*)
Colistimethate	Coly-mycin M	
Other		
Clindamycin	Cleocin	Prevalence of resistance to *B. fragilis* group
Metronidazole	Flagyl	Recommended in combination for patients with high-severity cIAI
Linezolid	Zyvox	VREF activity

Table 4: Currently Available Treatments for cUTI

Generic name	Trade name	Comments
Extended-spectrum penicillins		
Piperacillin	Pipracil	
Cephalosporins (parenteral 2nd, 3rd and 4th generation)		Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli
Cefotetan	Cefotan	
Cefoxitin	Mefoxin	
Cefuroxime sodium	Zinacef	
Cefotaxime	Claforan	
Ceftazidime	Fortaz, Tazicef	
Ceftriaxone	Rocephin	
Cefepime	Maxipime	
β-lactam/β-lactamase Inhibitor Combinations		
Ticarcillin clavulanate	Timentin	
Piperacillin-tazobactam	Zosyn	
Ceftolozane-tazobactam	Zerbaxa	
Fluoroquinolones		Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy
Levofloxacin	Levaquin	
Ciprofloxacin	Cipro	
Carbapenems		
Imipenem-cilastatin	Primaxin	
Ertapenem	Envanz	
Doripenem	Doribax	
Monobactams		Although used in pts with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime
Aztreonam	Azactam	
Aminoglycosides		Risk of nephrotoxicity and ototoxicity.
Gentamicin		
Amikacin		
Tobramycin		
Tetracyclines		
Minocycline	Minocin	
Polymyxins		Some gram-negatives are intrinsically resistant (e.g. *Proteus* spp. *Providencia* spp. Sereratia spp., B. cepacia), safety risks including nephrotoxicity and rare but serious neurotoxicity
Polymyxin B	Poly-Rx	
Colistimethate	Coly-mycin M	
Sulfa		
Trimethoprim-Sulfamethoxazole	Bactrim	IV formulation for "severe UTI"

2.3 Availability of Proposed Active Ingredient in the United States

Ceftazidime was approved for marketing in the US on 19 July 1985 under the trade name FORTAZ® (NDA 50578). The currently labeled indications, as described in the US package insert, are summarized in Table 5.

Fortaz is the referenced listed drug for ceftazidime. DMF (b) (4) is cross referenced by this NDA for the CAZ-AVI CMC information. Drug products with ceftazidime as the active ingredient are

available only for parenteral administration. Manufactured strengths include 500 mg/vial, 1 g/vial, 2 g/vial and 6g/vial (bulk). Generic and pre-mixed solutions have also been approved and are listed in Table 6.

Table 5: Currently Labeled Clinical Indications for Ceftazidime

Indication	**Pathogens**
Lower respiratory tract	*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	*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	*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	*E. coli*
Intra-abdominal	*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	*H. influenzae*, *N. meningitidis,* and limited: *P. aeruginosa, S. pneumoniae*

Table 6: Approved Ceftazidime Drug Products with Therapeutic Equivalence Evaluations

Application Number	**RLD**	**Active Ingredient**	**Strength**	**Proprietary Name**	**Applicant**
ANDA 062640	No	Ceftazidime	1 gm/vial	Ceftazidime	ACS Dobfar
ANDA 062640	No	Ceftazidime	2 gm/vial	Ceftazidime	ACS Dobfar
ANDA 062640	No	Ceftazidime	500 mg/vial	Ceftazidime	ACS Dobfar
ANDA 062640	No	Ceftazidime	6 gm/vial	Ceftazidime	ACS Dobfar
ANDA 065196	No	Ceftazidime	1 gm/vial	Ceftazidime	Wockhardt
NDA 050823	No	Ceftazidime	Eq 1 gm base	Ceftazidime in Dextrose Container	B Braun
NDA 050823	Yes	Ceftazidime	Eq 2 gm base	Ceftazidime in Dextrose Container	B Braun
NDA 050578	Yes	Ceftazidime	1 gm/vial	Fortaz	Covis Injectables
NDA 050578	Yes	Ceftazidime	2 gm/vial	Fortaz	Covis Injectables
NDA 050578	Yes	Ceftazidime	500 mg/vial	Fortaz	Covis Injectables
NDA 050578	Yes	Ceftazidime	6 gm/vial	Fortaz	Covis Injectables
ANDA 062662	No	Ceftazidime	1 gm/vial	Tazicef	Hospira
ANDA 064032	No	Ceftazidime	1 gm/vial	Tazicef	Hospira
ANDA 064032	No	Ceftazidime	2 gm/vial	Tazicef	Hospira
ANDA 062662	No	Ceftazidime	2 gm/vial	Tazicef	Hospira
ANDA 062662	No	Ceftazidime	500 mg/vial	Tazicef	Hospira
ANDA 062662	No	Ceftazidime	6 gm/vial	Tazicef	Hospira
NDA 050634	Yes	Ceftazidime sodium	Eq 20 mg base/mL	Fortaz in Plastic Container	Covis Injectables
NDA 050634	Yes	Ceftazidime sodium	Eq 40 mg base/mL	Fortaz in Plastic Container	Covis Injectables

Avibactam is a new chemical entity that is not previously or currently marketed in the US or other country, either alone or in combination.

2.4 Important Safety Issues with Consideration to Related Drugs

Serious adverse reactions associated with the cephalosporin-class include colitis, toxic nephropathy, hepatic dysfunction (including cholestatic jaundice), aplastic anemia, hemorrhage. Neurological adverse reactions, including seizures and convulsions, may occur with high CNS levels, particularly in the setting of renal impairment. 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 list of currently approved BL-BLI drugs is shown below in Table 7. These combinations are generally well-tolerated; however, the most commonly reported reasons for drug discontinuation include skin reactions (including rash and pruritus) and gastrointestinal reactions (including diarrhea, nausea, and vomiting). All BL-BLI combinations are primarily excreted through the kidneys and require dosage adjustment with impaired renal function.

Table 7: Currently Approved β-lactam/β-lactamase Inhibitor Combinations

Generic name	Trade name	Year of approval
Amoxicillin clavulanate	Augmentin	1984
Ticarcillin clavulanate	Timentin	1985
Ampicillin-sulbactam	Unasyn	1986
Piperacillin-tazobactam	Zosyn	1993
Ceftolozane-tazobactam	Zerbaxa	2014

ZERBAXA™, a combination of ceftolozane (a semi-synthetic cephalosporin) and tazobactam, was approved on 19 December 2014 for the treatment of cIAI and cUTI. The Zerbaxa label includes a warning about decreased efficacy in patients with baseline CrCL of 30 to ≤50 mL/min and recommends that patients with changing renal function should be monitored at least daily with the dose adjusted accordingly. In clinical trials the most common ADRs identified in the clinical trials were nausea, diarrhea, headache and fever (pyrexia). Renal impairment led to discontinuation of treatment in 5/1015 (0.5%) subjects receiving Zerbaxa versus none in the comparator arms.[3]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial 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. Forest was acquired by Actavis in February 2014. Cerexa and AstraZeneca are now collaborative partners for the global development of CAZ-AVI, with Cerexa having responsibilities for the US development rights. Of note, in 2011 Covis Pharma acquired full U.S. commercial rights from GlaxoSmithKline for Fortaz, the Reference Listed Drug (RLD) for ceftazidime.

The FDA has had several pre-submission discussions with the Applicant regarding their Phase 3 clinical development program. On 11 March 2013, the FDA 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 FDA 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. Key interactions between the Sponsor and FDA are summarized as follows in Table 8.

Table 8: Key Regulatory Interactions Regarding CAZ-AVI Development

Date	***Type of Interaction***
07 Jan 2008	Original IND submitted by Novexel SA
16 Apr 2010	IND Ownership transferred to AstraZeneca Pharmaceuticals
18 Oct 2010	Type C Meeting to discuss development program
07 Mar 2011	Type B EOP2 Meeting to discuss Phase 3 development strategy in cIAI and cUTI
16 Jun 2011	EOP2 Follow-up teleconference to further discuss details of cIAI and cUTI Phase 3 study designs
06 Jul 2011	FDA written correspondence to follow-up from 16 Jun 2011 teleconference with non-inferiority margin justification for cIAI
13 Sep 2011	FDA Written Advice/Information Request regarding cIAI and cUTI study design
05 Oct 2011	IND Ownership transferred to Cerexa, Inc. (a subsidiary of Forest Laboratories, Inc.)
11 Mar 2013	QIDP and Fast Track Designations for cIAI, cUTI and HABP/VABP
17 Jun 2013	Type C Meeting to discuss changes to cIAI and cUTI Phase 3 program, discuss filing strategy for the early registration of CAZ-AVI for the treatment of subjects with serious bacterial infections and limited treatment options
19 Dec 2013	Type B Pre-NDA Meeting to discuss the format and filing of an NDA for CAZ-AVI based upon nonclinical data, Phase 1 data, data from two Phase 2 studies, and published ceftazidime data
30 Jan 2014	Type B Pre-NDA CMC Meeting (meeting cancelled due to adequate written response) (FDA preliminary comments dated 24 Jan 2014)

Adapted from the Applicant's Table 3-1, Section 1.2, Sponsor's Reviewer Guide.

As discussed with the Applicant during the pre-NDA phase, this application utilizes the 505(b)(2) pathway and relies on the FDA's prior finding of safety and effectiveness of ceftazidime, as well as published historical data. Because CAZ-AVI is a fixed drug combination and confirmatory clinical trials comparing ceftazidime alone to CAZ-AVI would not be feasible, the contribution of both components under the requirements of 21 CFR § 300.50 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 CAZ-AVI-treated subjects with ceftazidime-nonsusceptible pathogens could be used describe the contribution of avibactam as well.

2.6 Other Relevant Background Information

CAZ-AVI is not currently marketed in any country. Avibactam sodium is an NCE and has not been previously approved in any other new drug combination. The Applicant has claimed ten years exclusivity for ceftazidime pentahydrate and avibactam sodium combination (CAZ-AVI),

which contains 2 grams ceftazidime pentahydrate and 0.5 grams avibactam sodium as the active ingredients. In addition to the five-year exclusivity, CAZ-AVI was also designated as a qualified infectious disease product (QIDP), which provides eligibility for an additional five years of exclusivity under Title VIII of FDA Safety and Innovation Act (Generating Antibiotic Incentives Now, or GAIN), Section 505E(a).

The Applicant has also submitted a Paragraph I Certification, which certifies that patent information, with respect to each patent issued by the United States Patent and Trademark Office that claims ceftazidime pentahydrate on which investigations that are relied upon by the Applicant for approval of this NDA were conducted or that claims an approved use for ceftazidime pentahydrate and for which information is required to be filed under Section 505(b) and (c) of the Federal Food Drug and Cosmetic Act and 21 CFR §314.53, has not been submitted to FDA.

Accompanying the proposed labeling and exclusivity request, the Applicant also submitted a request for a proprietary name review for "Cazavi".

Medical Officer comment: Although ceftazidime-avibactam has been referred to as "CAZ-AVI" and has gained familiarity with this name during the late stages of development, the Division of Medication Error Prevention and Analysis (DMEPA) reviewed this proprietary name request and found that "Cazavi" was unacceptable due to orthographic similarities and shared product characteristics with the proprietary name Cozaar®. The alternative proposed proprietary name, "Avycaz", however, was also reviewed and considered acceptable.

3 Ethics and Good Clinical Practices

This NDA package was submitted in eCTD format in accordance with the electronic format of the M4 International Conference on Harmonization (ICH) Common Technical Document (CTD). Included is a Review's Guide that summarizes the format of the clinical datasets. Upon initial review of the package, all of the datasets were included, with the exception TE, TI, TS, TV, VS, and XC for Study NXL104/2001, which was likely due to a transfer error. The Applicant resubmitted the entire tabulation data package for this study on 10 July 2014.

The sites chosen for inspection were based on high enrollment in order to provide review for sites from each indication/pivotal trial, as well as both domestic and international (Table 9).

Table 9: Clinical Investigation Sites Chosen for Routine Inspection

	NXL104/2001	NXL104/2002
International	Site #400 Luis Gonzalez 15 subjects, Santa Rosita, Guatemala	Site #64 Mayakonda Ramesh, M.D. 26 subjects, Bangalore, India
Domestic	Site #113 Salahuddin Bibi, M.D. 6 subjects, Modesto, CA	Site #12 Christopher Lucasti, DO 10 subjects, Somers Point, NJ

Since this application is a 505(b)(2) with no rigorous statistical inference testing planned, there was no initial concern that one particular site could potentially drive efficacy results. Upon preliminary review, there were no specific safety signals; however, concerns for GCP compliance arose with the cIAI trial (NXL104/2002), for which Novexel (the former sponsor before Cerexa) conducted an audit to look into several potential issues with the IVRS provided by a CRO called (b) (4). Novexel's unblinded medical reconciliation found that validity of randomization was maintained, but auditors concluded that the violations were "critical".

3.1 Submission Quality and Integrity

The structure and content of Modules 2 and 5 were discussed and agreed to with the FDA at the Type B Pre-NDA Meeting held on 19 Dec 2013.

There are two separate Integrated Summaries of Efficacy (ISE) for cIAI and cUTI that include written summaries located in Module 2.7.3 - cIAI and Module 2.7.3 - cUTI with appendices and supporting tables located in Module 5.3.5.3.

The Integrated Summary of Safety (ISS) includes a written summary located in Module 2.7.4 with appendices and supporting tables located in Module 5.3.5.3.

Medical Officer comment: Prior to submission of this NDA, the Applicant provided sample datasets for both of their Phase 2 trials to the IND (IND-101307). The JumpStart Team in the Computational Science Center conducted a data fitness evaluation. Recommendations to correct non-standard CDISC coding, or where there may have been missing data, were returned to the Applicant.

Overall, the documents and data provided in this submission were of adequate quality. However, the naming of the variables was not consistent among datasets in the two Phase 2 studies. For example, in some datasets the subject ID was concatenated with the Study ID and the Site ID to form the unique subject ID while in some the subject ID was the unique subject ID. Field names are also not consistent across trials. These made it difficult to replicate analysis from one study to another. For trial NXL-104-2002, values for the standard reference ranges (LBSTNRLO and LBSTNRHI) were not provided in the LB dataset. ULN values were more difficult to use for standard analyses, since original units were not completely consistent for each test. A response to the Division's Information Request sent on 11 Aug 2014 was received on 01 Oct 2014 and provided additional analyses as well as references to the location of requested data submitted in the original submission.

3.2 Compliance with Good Clinical Practices

For the cIAI trial (NXL104-2002), Novexel conducted an audit to look into several potential compliance issues due to errors with IVRS provided by a CRO called (b) (4). Novexel's unblinded medication reconciliation found that validity of randomization was maintained, but

their independent auditors concluded that the violations were "critical". (b) (4) has not previously been inspected by the FDA. The preliminary FDA inspection classification was Voluntary Action Indicated (VAI), primarily related to monitoring practices during the course of the study. Problems with the IVRS randomization and assignment of study drug vials were not acted upon promptly; however, the Sponsor did go through an extensive drug reconciliation process to ensure that subjects received appropriate study drug treatment.

For Study NXL104/2001 (cUTI), a domestic (Dr. Bibi) and foreign (Dr. Gonzalez) site were selected for inspection based upon enrollment numbers. The preliminary classification for both inspections was VAI. For Dr. Gonzalez, Test of Cure urine cultures at this site were not obtained within the appropriate timeframe and the results of those cultures may have been potentially impacted by subjects' oral antibiotic regimen. For Dr. Bibi, the ORA investigators noted that the all six subjects received a dose of potentially effective systemic antibiotic after the baseline urine culture was obtained and before the subject was randomized.

Medical Officer comment: Administration of prior antibacterial treatment is not unexpected, particularly in the US, where at least one empiric dose of a 3rd generation cephalosporin, such as ceftriaxone, is common practice once the diagnosis is made. Ideally, however, no more than 25% of all subjects in a cUTI should get a potentially effective dose. Although this may confound findings of efficacy, especially with the IV to oral switch to ciprofloxacin option, upon review of other sites outside of the US, receipt of an antibiotic prior to initiation of the study drug was not common.

For Study NXL104/2002 (cIAI), a domestic (Dr. Lucasti) and a foreign (Dr. Ramesh) clinical site inspection were requested. The inspection of Dr. Ramesh in India was scheduled to occur February 2-6, 2015 and results are pending. The preliminary classification for Dr. Lucasti's site is No Action Indicated (NAI).

3.3 Financial Disclosures

Clinical investigators who enrolled subjects in studies NXL104/2001 or NXL104/2002 and who have no disclosable financial arrangements (grouped by study) were provided in an attachment to form FDA 3453. The Applicant certifies that the financial information described meets requirements in 21 CFR § 54.4.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Key elements of the nonclinical development program for CAZ-AVI are summarized below in Table 10.

Table 10: Overview of the Nonclinical Development Program for CAZ-AVI

In Vitro Microbiology

- Against key organisms that cause cUTI and cIAI
- Hollow fiber models

Animal Infection Models

- Bacterial clearance from target organs and survival in murine and rabbit models of infection (pneumonia, pyelonephritis, meningitis, systemic infection, and thigh infection)

Pharmacokinetics and Drug Metabolism

- Non-clinical ADME of avibactam
- Exposure levels of CAZ-AVI required to achieve efficacy

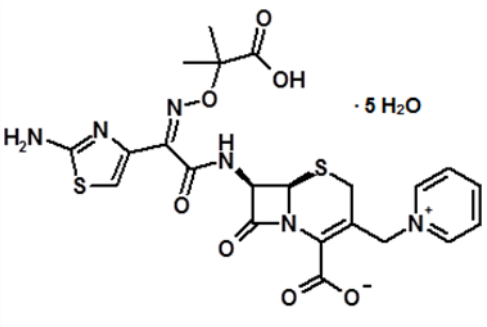
Toxicology Studies (avibactam alone and in combination with ceftazidime)

- Avibactam alone up to 3 months in rats and dogs
- Safety pharmacology
- Genetic toxicology
- Reproductive (male and female fertility in rats, embryofetal development in the rat and rabbit)
- Immunotoxicology
- Local tolerance studies
- In vitro phototoxicity study

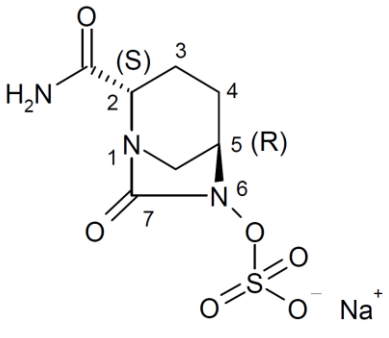
4.1 Chemistry Manufacturing and Controls

The drug product, ceftazidime and avibactam for injection is supplied as a white to yellow sterile powder in a single use, sterile, clear glass vial containing 2 grams of ceftazidime (equivalent 2.635 grams of ceftazidime pentahydrate/sodium carbonate powder) and 0.5 grams of avibactam (equivalent to 0.551 grams of avibactam sodium). Chemical structures are shown in Figure 1.

Figure 1: Chemical Structures of Ceftazidime Pentahydrate and Avibactam Sodium



Ceftazidime Pentahydrate



Avibactam Sodium

The chemical name of ceftazidime is (6R,7R,Z)-7-(2-(2-aminothiazol-4-yl)-2-(2-carboxypropan-2-yloxyimino)acetamido)-8-oxo-3-(pyridinium-1-ylmethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate. Its molecular weight is 636.6. The empirical formula is $C_{22}H_{32}N_6O_{12}S_2$. For avibactam sodium the chemical name is sodium [(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate. Its molecular weight is 287.23. The empirical formula is $C_7H_{10}N_3O_6SNa$.

Ceftazidime pentahydrate is included in the form of the commercially available ceftazidime pentahydrate-sodium carbonate blend. Avibactam sodium is manufactured as a single drug substance. The ceftazidime carbonate blend and avibactam sodium are (b) (4)

In-use stability and compatibility studies for the reconstituted drug product including evaluation of the drug product with common infusion diluents, intravenous (IV) bags and infusion lines have also been conducted. The stability data for the drug product currently support a shelf life of 24 months at room temperature. Potential genotoxic impurities (b) (4) (b) (4) are controlled through in process control and estimated well below the threshold of toxicology concern (TTC) level in the avibactam sodium batches. The impurity (b) (4) is qualified at (b) (4)% as proposed in the drug substance specification and (b) (4)% in the drug product specification.

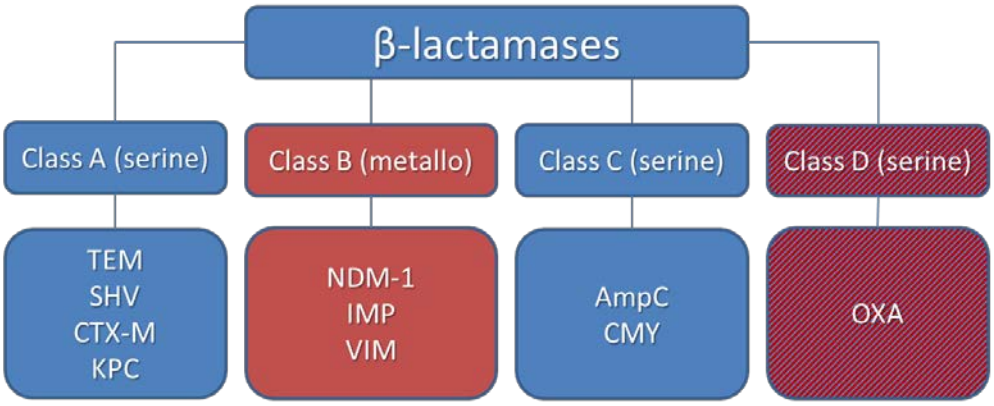
Medical Officer comment: Inspection of the manufacturers and facilities was requested through the Establishment Evaluation System (EES). One of the active ingredient manufacturers for avibactam starting material and intermediate was (b) (4) Upon approval, however, the Applicant will use avibactam starting material and avibactam intermediate from (b) (4) respectively. The CMC reviewer for this NDA is Zhengfang Ge, PhD, and the Product Quality Microbiology reviewer is Robert Mello, PhD. According to Dr. Ge, the Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. From a product quality microbiology perspective Dr. Mello recommends approval as well. Please refer to their reviews for additional detail.

4.2 Clinical Microbiology

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. Avibactam is a diazabicyclooctanone, non-β-lactam β-lactamase inhibitor with activity across multiple serine-based β-lactamase classes (Figure 2). Although avibactam alone has no direct antibacterial activity (at concentrations achieved in humans at the proposed dose), 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*. Against Enterobacteriaceae CAZ-AVI demonstrates activity against Class A, C and some Class D ESBL producing isolates.

Figure 2: Classes of β-lactamases and BLI Activity



While other BL/BLI combinations have been approved (Table 7), the activity of these combinations do not include Ambler Class A KPCs, Class B enzymes (metallo-β lactamases, e.g. NDM-1), Class C enzymes (e.g. AmpC) and may induce ESBL production. Avibactam, however, provides additional inhibition of Class A ESBLs, KPCs, AmpC, and some Class D enzymes, but is not active against the metallo-β lactamases (Class B).

Preclinical studies with CAZ-AVI provide supportive evidence for antibacterial activity against the common gram-negative pathogens causing serious bacterial infections. The activity of CAZ-AVI was assessed against Enterobacteriaceae and *P. aeruginosa* isolates associated with cIAI and cUTI.

Table 11 shows microbiological surveillance data with gram-negative bacterial isolates collected from 73 US medical centers from patients with cUTI, and Table 12 shows data from patients with cIAI. CAZ-AVI was active against a collection of ceftazidime non-susceptible Enterobacteriaceae and some meropenem non-susceptible *P. aeruginosa*.

Table 11: 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

Source: Table 1.5.2–1, Module 2.5 Clinical Overview

Table 12: 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

Source: Table 1.5.1–1, Module 2.5 Clinical Overview

For the purpose of their analysis, the Sponsor identified CAZ-NS isolates as those that were either ceftazidime-resistant (CAZ-R) (minimum inhibitory concentration [MIC] ≥ 16 mg/L for Enterobacteriaceae; MIC ≥ 32 for *P. aeruginosa*) or ceftazidime-intermediate (CAZ-I) (MIC ≥ 8 mg/L and < 16 mg/L for Enterobacteriaceae; MIC ≥ 16 mg/L and < 32 for *P. aeruginosa*) using Clinical Laboratory Standards Institute (CLSI) methodology.[4] As of 24 September 2014, the following table (Table 13) shows the most current recommendations for ceftazidime based on the updated Fortaz USPI. [5]

Table 13: Susceptibility Test Interpretive Criteria for Ceftazidime

Pathogen	Minimum Inhibitory Concentrations (mcg/ml)			Disk Diffusion Zone Diameters (mm)		
	(S) Susceptible	(I) Intermediate	(R) Resistant	(S) Susceptible	(I) Intermediate	(R) Resistant
Enterobacteriaceae[§]	≤ 4	8	≥16	≥ 21	18-20	≤17
Haemophilus influenzae[a]	≤2	-	-	≥26	-	-
Pseudomonas aeruginosa[*]	≤ 8	-	≥ 16	≥ 18	-	≤ 17

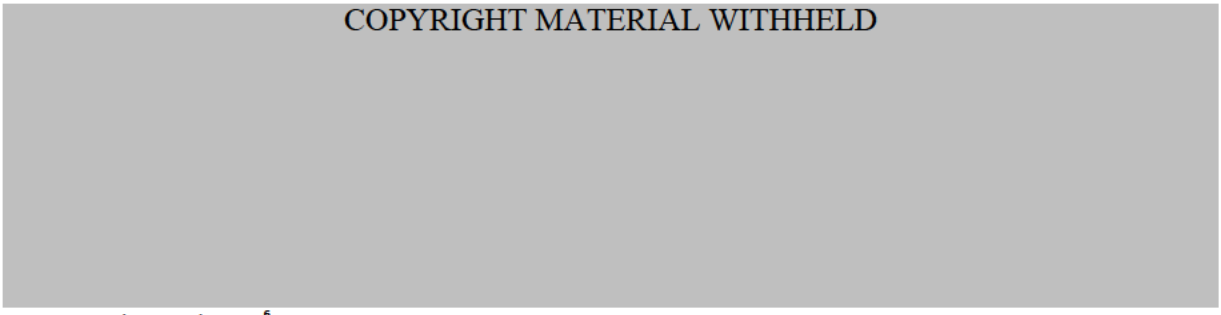
[§] Susceptibility interpretive criteria for Enterobacteriaceae are based on a dose of 1 gram q 8h. For isolates with intermediate susceptibility, use a dose of 2 grams every 8 hours in patients with normal renal function.
[a] The current absence of data on resistant isolates precludes defining any category other than 'Susceptible'. If isolates yield MIC results other than susceptible, they should be submitted to a reference laboratory for additional testing.
Susceptibility of staphylococci to ceftazidime may be deduced from testing only penicillin and either cefoxitin or oxacillin.
* For *P. aeruginosa*, susceptibility interpretive criteria are based on a dose of 2 grams IV every 8 hours in patients with normal renal function.

4.2.1 Mechanism of Action

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 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 3).

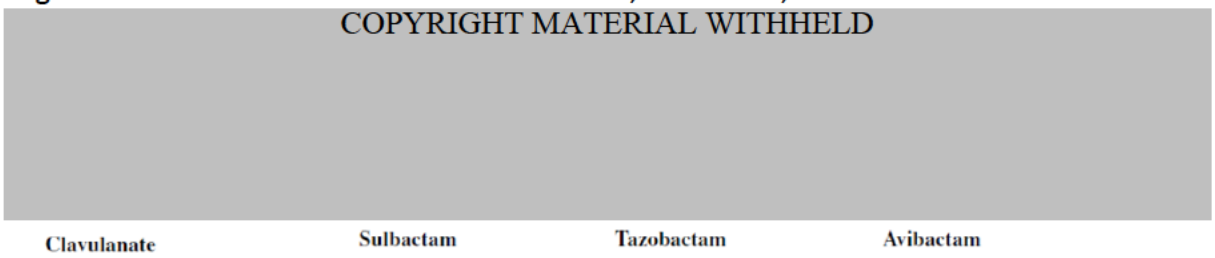
Figure 3: Proposed Molecular Mechanism of Action of Avibactam



Source: Stachyra et al. 2010.[6]

Avibactam differs from other β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam (Figure 4) in three key aspects.

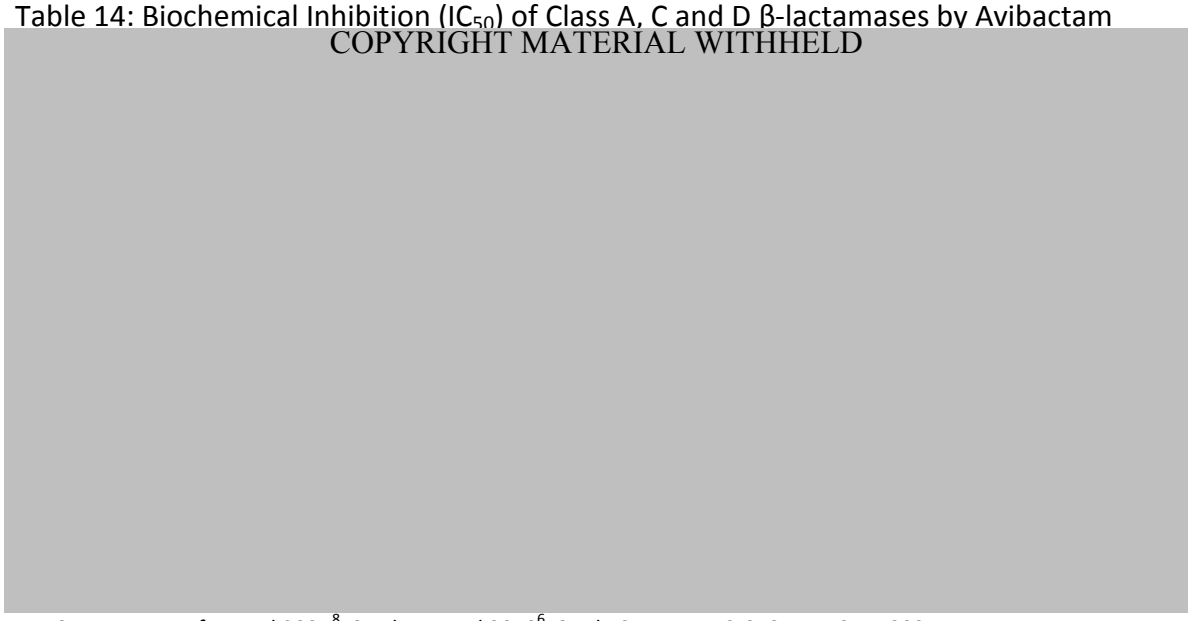
Figure 4: Chemical Structures of Clavulanic Acid, Sulbactam, Tazobactam and Avibactam



Source: Winkler et al. 2015[7]

First, 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 has improved inhibition over clavulanate, tazobactam, or sulbactam against Class A β-lactamases (TEM-1, SHV-4 and KPC-2) and Class C β-lactamases (AmpC) and has similar inhibition to tazobactam against class A (CTX-M-15). Against the single Class D enzyme tested (OXA-23), avibactam was more potent than tazobactam. Table 14 shows the biochemical inhibition (IC_{50}) of class A, C and D β-lactamases.

Table 14: Biochemical Inhibition (IC_{50}) of Class A, C and D β-lactamases by Avibactam



Source: Bonnefoy et al 2004[8], Stachyra et al 2010[6], Study CAZ-AVI-M2-018-NXL104-BI0001

4.2.2 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.

Medical Officer comment: Additional studies available in published literature were also reviewed. One study at Case Western in Cleaveland, OH (Winkler et al, 2015)[7] investigated a collection of β-lactam-resistant *P. aeruginosa* clinical isolates archieved > 10 years ago, of which 18.5% were found to be resistant to CAZ-AVI (defined as an MIC > 8 mg/L). Altered outer membrane permeability or overexpressed efflux pumps were found to be important mechanisms. For most of these isolates combination with fosfomycin lowered MICs below the breakpoint. Financial support for this study was provided in part by AstraZeneca.

4.2.3 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. As summarized in Table 15, 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.

Table 15: Overview of Animal Models of Infection

Disease Model and Animal	Results	Pathogens
Systemic infection Immune-competent mice	Survival with CAZ: ED_{50} >50 mg/kg CAZ-AVI: ED_{50} 5 to 29 mg/kg	Class A and Class C Enterobacteriaceae
Pneumonia Immune-compromised mice	Bacterial clearance* in the lung (↓5-6 log_{10}), untreated animals developed bacteremic pneumonia died within 2-4 days	48 hr post infection 10^{11} CFU/g of lung tissue *K. pneumoniae* (ESBL)
Pyelonephritis Immune-compromised mice	Bacterial clearance* in kidney (↓2.6 to 4.5 log_{10})	48 hr post infection 10^5 to 10^7 CFU/kidney (ESBL/AmpC) *K. pneumo, E. coli, E. cloacae, M. morganii, C. freundii*
Meningitis Immune-competent Rabbit	Bacterial clearance* in CSF >5 log_{10} reduction at 8 h	*K. pneumoniae* (AmpC)
Thigh infection Immune-compromised mice	CAZ:↓bacterial load by >0.5 log_{10} for 10/27 isolates, CAZ-AVI: ↓load for 22/27	*K. pneumoniae* (KPC) *P. aeruginosa*

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

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 to < 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.

Medical Officer comment: Of note, these studies of CAZ-AVI in animal models of infection were not validated, conducted without GLP specification, and not intended to be conducted for development under the Animal Rule (21 CFR 314.600). For example, it was not clear from that the methods used for the delivery of the challenge agent and trigger for initiation of treatment ensured adequate standardization, replication of test conditions and comparability between treatment arms. Ultimately, the natural histories of the infections used in these models may not necessarily have had sufficient similarities to extrapolate to humans. Notwithstanding the limitations in interpretation of the results, these studies (i.e. ceftazidime vs. CAZ-AVI in infections caused by clinically relevant CAZ-NS pathogens) would not be feasible in humans and help provide additional supportive evidence of the contribution of avibactam. Please also refer to the Clinical Microbiology review, including recommendations for labeling and post-marketing surveillance, by Avery Goodwin, PhD for further details. According to his review, the Applicant provided sufficient data to support approval.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical studies primarily addressed the pharmacology and toxicity of avibactam alone; however, studies with the combination of avibactam with ceftazidime were also conducted in rats and dogs.

The half-life of avibactam in rats and dogs ranged between 3 and 10 hours. Plasma levels did not significantly affect ceftazidime plasma levels, while ceftazidime did not significantly alter avibactam plasma levels. Protein binding of avibactam was low in humans, mice, rats, rabbits and dogs (all less than 25% by an ultracentrifugation method and approximately 8.2% bound in human plasma). Distribution was primarily into the kidney and bladder in the first few hours following injection. In separate tissue distribution studies, avibactam was also detected in CSF and lung epithelial lining fluid (ELF) of mice at exposures lower than plasma. Avibactam penetration into the brain or across the placenta was minimal. There was no evidence of accumulation in either species after multiple doses and exposure in males and females was comparable. Metabolism as measured by exposure to liver microsomal preparation or as measured in the urine and plasma of rats, dogs and humans was minimal. Avibactam did not

stimulate or inhibit cytochrome P450 enzymes or transporter proteins. 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. The primary route of excretion was urine; fecal elimination accounted for 17% of the dose in rats, 5% in dogs, and <1% in rabbits.

The toxicity of avibactam was investigated in mice, rats, and dogs. In single dose studies, intravenous administration of up to 2000 mg/kg was a NOAEL in rats and mice. Similarly, a single oral gavage dose of 2000 mg/kg was also a NOAEL in rats and mice. Administration to rats or dogs for 4 or 13 weeks primarily caused damage to the injection site. In 4-week combination studies CAZ-AVI (using the 4:1 ratio), toxicity was injection site damage. Some evidence of liver damage was also seen in the dog. The 13-week rat study with avibactam was difficult to interpret due to infection from the catheters. Dogs showed only injection site damage. At intravenous doses of up to 1000 mg/kg as a single administration, avibactam had minimal effects on behavior, gastrointestinal transit, blood pressure, heart rate, QT interval, or neurologic, renal or respiratory function. A hERG assay was negative.

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. The rat peri- and post-natal toxicity study showed an increase in the incidence of dilated pelvis and dilatation of the ureter by both individual pups and litter at the high dose of 825 mg/kg/day.

Avibactam was studied for genetic toxicity with the Ames assay, unscheduled DNA synthesis, mouse lymphoma clastogenicity, human lymphocyte chromosomal abberations, and rat micronucleus assays. All were negative. Ceftazidime was previously investigated, and as described in the Fortaz label, the Ames test and a mouse micronucleus assay were negative. No teratogenic effects in mice or rabbits at doses of 6.5 g/kg/day and 0.2 mg/kg/day, respectively. Carcinogenicity testing was not conducted based on the brief duration of use.

The nonclinical toxicities of ceftazidime were described in published literature. Liver and kidneys were shown to be a target in rats with high doses over at least a month of dosing. Both intravenous and subcutaneous routes of dosing showed little difference in toxicity and toxicities were reversible. Dogs were reported to show no toxicity at doses (route of administration not specified) up to 540 mg/kg/day for 30 days.[9]

Medical Officer comment: Overall, with avibactam alone, there was minimal toxicity noted in rats or dogs with 4- or 13-week studies at doses up to 1000 mg/kg/day by the intravenous route. Studies in rats and dogs at one month with the combination of avibactam and ceftazidime did not demonstrate any new toxicities or significantly more severe toxicity than with ceftazidime alone. Please also refer to the Pharmacology/Toxicology review by Wendelyn Schmidt, PhD for further details. According to her review, the Applicant provided sufficient non-clinical data to recommend approval for CAZ-AVI.

4.4 Clinical Pharmacology

Ten Phase 1 studies have been completed with avibactam alone or CAZ-AVI, including a study to assess the penetration of ceftazidime and avibactam into the epithelial lining fluid (ELF) of healthy subjects (D4280C00009), a study to determine if there was a drug-drug interaction (DDI) between ceftazidime and avibactam (D4280C00011), and a study to determine if there was a DDI between CAZ-AVI and metronidazole (D4280C00012). Ceftazidime pharmacokinetic (PK) data are available from seven of the Phase 1 CAZ-AVI studies and the two Phase 2 CAZ-AVI studies. The basic PK properties of ceftazidime are also cited in the approved drug label (Fortaz® US Prescribing Information) and published literature.[5]

4.4.1 Mechanism of Action

Please refer to Clinical Microbiology sections 4.2.1 and 4.2.2.

4.4.2 Pharmacodynamics

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 was estimated at 0.5 mg/L from 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 restoration of ceftazidime activity against ceftazidime-resistant *P. aeruginosa* in neutropenic mouse thigh and lung infection models. Using the maximal dose of ceftazidime that would allow background 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 maintain 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 16, with target attainment by renal function group at the proposed dose regimen.

Table 16: 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

4.4.3 Pharmacokinetics

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.

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 17. 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 17: 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 18).

Table 18: 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 ($p > 0.2$)

Medical Officer comment: Please refer to Section 7.7 for presentation and discussion of amended data from the Phase 3 cIAI trial. Please also refer to the Clinical Pharmacology review by Seong Jang, PhD for further details. According to his review, the Applicant provided sufficient data to recommend approval for CAZ-AVI pending changes to the proposed labeling for renal dosing adjustments and an associated post-marketing requirement to confirm CAZ-AVI exposure estimates and correlate with efficacy and safety in patients with cIAI and baseline CrCl < 50 mL/min in an open-label study using the amending doses.

5 Sources of Clinical Data

Thirteen clinical studies of CAZ-AVI or avibactam alone have been completed (Table 19). This includes 11 completed Phase 1 Clinical Pharmacology studies (10 from the CAZ-AVI development program, and 1 from the ceftaroline fosamil-avibactam [CXL] program) and 2 completed Phase 2 efficacy and safety studies in cIAI and cUTI. Additionally there are 8 ongoing CAZ-AVI studies (Table 20).

5.1 Tables of Studies/Clinical Trials

Table 19: 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 20: Ongoing Clinical Studies

Study ID	**Study Type/Population**	**Blinded**
Phase 3 Clinical Efficacy and Safety Studies		
D4281C00001	HABP/VABP/Infected hospitalized adults	yes
D4280C00001/5[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).
[b] Subjects enrolled under identical study protocols D4280C00002 and D4280C00004 are combined into one study database (D4280C00002/4).

5.2 Review Strategy

At a CDER Regulatory Briefing held 29 May 2009, the panel discussed the "Combination Rule" (i.e. demonstrating the contribution of each component in a combination under the requirements of 21 CFR § 300.50) as it applies to a proposed BL-BLI combination product. When confirmatory clinical trials comparing the β-lactam alone to the combination product are not feasible, the panel concluded that there are other ways to reach the conclusion that both components contribute, such as supportive data from in vitro microbiology, PK/PD models, and animal studies. Evidence from subgroups of patients with resistant pathogens can be described as well, when the BL-BLI combination is compared to the standard-of care.

Given that this application was submitted via the 505(b)(2) pathway, where the review of relies upon the previous finding of safety and efficacy for ceftazidime, non-clinical data and animal models can be considered supportive in the demonstration the contribution of avibactam. Demonstration of efficacy in human clinical trials will be reviewed for each clinical indication being sought with emphasis on subgroups of patients with infections caused by ceftazidime-resistant organisms.

For the overall approach of this review, individual clinical pharmacology studies from Phase 1 will be reviewed in Section 5.3, because the study objectives of each study varied with regard to dose ranges, study design and included avibactam, either alone or in combination with ceftazidime or ceftaroline. Discussion of results from these trials will focus on clinical safety assessments rather than pharmacology, as the review of clinical pharmacology is summarized in Section 4.4. The review of integrated safety and efficacy data, including analyses of the two Phase 2 clinical trials and preliminary data from the open-label Phase 3 trial (Resistant Pathogen Study), will be discussed in the respective subsections within Section 6, and Section 7. The requested indication for HABP/VABP and bacteremia is not accompanied by clinical data from any well-controlled trial. For the purposes of this review, rather than evaluating efficacy for the indication requested, the interim data presented from the Resistant Pathogen Study will be covered separately in Section 6.3 as supportive descriptive evidence for the requested indications of cIAI and cUTI.

The majority of comparative safety data reviewed (i.e., adverse event rates) were from two Phase 2 trials. Pooling, however, between these two trials is not appropriate for most safety analyses due to the differences in the patient population and diseases being studied. Subjects in Trial 2002 (cIAI) were peri-operative with higher risk of surgical complications, prolonged hospital stay and mortality, whereas subjects in Trial 2001 (cUTI) received a dose 25% of what is currently recommended for both indications. Dosing recommendations (including a 2-hour infusion time, rather than 30 minutes) were based on PK modeling from Phase 2 data, and have only been studied prospectively in Phase 3 trials. Additional review of renal dosing adjustments based on preliminary data from the Phase 3 cIAI trial will be covered in Section 7.7.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study NXL104/1001

Primary objective: To investigate the safety and tolerability of escalating single intravenous doses (from 50 to 2000 mg) of avibactam administered alone and in combination with ceftazidime (2 doses) in healthy volunteers.

Secondary objective: To investigate the pharmacokinetics of avibactam administered alone (single intravenous doses of 50 to 2000 mg) and in combination with ceftazidime (2 doses: 250mg avibactam + 1000mg ceftazidime and 500mg avibactam + 2000mg ceftazidime) in healthy volunteers.

Study dates: 15 November 2006 to 20 February 2007

Study design: This study was an escalating dose study (except for subjects of groups 3 and 4 who received a 2nd dose of avibactam in combination with ceftazidime) using a randomized, double-blind, placebo-controlled design in 7 dose groups of healthy young adults male subjects (10 subjects per dose group, 8 active and 2 placebo).

There was a 21-day screening period, a baseline period (D-1), followed by a single intravenous infusion and a completion visit between 7 and 9 days after dosing. Subjects of groups 3 and 4 received a 2nd dose of avibactam in combination with ceftazidime after a wash out period of 7 days.

Two doses were tested in combination (avibactam + ceftazidime) in a design (avibactam alone then avibactam + ceftazidime) separated by a wash-out period of 7 days:

- 250 mg avibactam + ceftazidime 1000mg, and
- 500 mg avibactam + ceftazidime 2000mg.

Each subject received only one dose, except for the combination avibactam + ceftazidime where subjects (i.e. 20 subjects) participated in 2 randomized sequential sessions: one with avibactam alone, one with the combination avibactam + ceftazidime.

Decision to go to the next dose level was based on safety and tolerability results (AEs reporting, safety laboratory results, local and general tolerability, clinical results) and if possible, pharmacokinetic data from at least 8 out of 10 subjects.

Results: A total of 117 volunteers were screened. Forty-seven were not included (most due to withdrawal of consent or abnormal lab values). Seventy (70) subjects were administered with the planned dose:

- 10 subjects received one dose of placebo
- 4 subjects received two doses of placebo
- 40 subjects received one dose of avibactam (50, 100, 1000, 1500 or 2000 mg)
- 8 subjects received one dose of avibactam 250 mg alone followed by one dose of avibactam 250 mg with one dose ceftazdime 1000 mg

- 8 subjects received one dose of avibactam 500 mg alone followed by one of avibactam 500 mg with one dose ceftazdime 2000 mg

All 70 subjects were males; 49 were Caucasian (70.0%), 13 were black (18.6%), 1 was Asian (1.4%) and 7 of other ethnic origin (10.0%). Subjects were 18 to 45 years old, with a mean (±SD) age value of 29.6 (±6.9) years.

No deaths, adverse events leading to treatment discontinuation, serious adverse events or severe adverse events were reported during this study and no subjects discontinued from the study. A total of 6 TEAEs were reported by 4/70 subjects (5.7%) in the 250, 500 and 2000 mg (avibactam alone) treatment groups. These TEAEs were mild or moderate in intensity and recovered without corrective treatment. A summary of subjects presenting with at least one TEAE by SOC and Preferred Term is shown in Table 21.

Table 21: Study NXL104/1001 - Summary of subjects presenting with at least one TEAE by SOC and Preferred Term

Subject with at least 1 TEAE	**Total (N=70)**	**Placebo (N=14)**	**Avibactam 50 mg (N=8)**	**Avibactam 100 mg (N=8)**	**Avibactam 250 mg (N=8)**	**Avibactam 250 mg + CAZ 1000 mg (N=8)**	**Avibactam 500 mg (N=8)**	**Avibactam 500 mg + CAZ 2000 mg (N=8)**	**Avibactam 1000 mg (N=8)**	**Avibactam 1500 mg (N=8)**	**Avibactam 2000 mg (N=8)**
System Organ Class Preferred term	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)	Subj. (%)
Total	**4 (5.7%)**	**-**	**-**	**-**	**2 (25.0%)**	**-**	**1 (12.5%)**	**-**	**-**	**-**	**1 (12.5%)**
Gastrointestinal Disorders	1 (1.4%)	-	-	-	1 (12.5%)	-	-	-	-	-	-
Abdominal Pain	1 (1.4%)	-	-	-	1 (12.5%)	-	-	-	-	-	-
General Disorders And Administration Site Conditions	1 (1.4%)	-	-	-	-	-	1 (12.5%)	-	-	-	-
Sense of Oppression	1 (1.4%)	-	-	-	-	-	1 (12.5%)	-	-	-	-
Nervous System Disorders	1 (1.4%)	-	-	-	-	-	1 (12.5%)	-	-	-	-
Somnolence	1 (1.4%)	-	-	-	-	-	1 (12.5%)	-	-	-	-
Psychiatric Disorders	1 (1.4%)	-	-	-	1 (12.5%)	-	-	-	-	-	-
Anxiety	1 (1.4%)	-	-	-	1 (12.5%)	-	-	-	-	-	-
Vascular Disorders	2 (2.9%)	-	-	-	1 (12.5%)	-	-	-	-	-	1 (12.5%)
Dizziness Postural	1 (1.4%)	-	-	-	1 (12.5%)	-	-	-	-	-	-
Orthostatic Hypotension	1 (1.4%)	-	-	-	-	-	-	-	-	-	1 (12.5%)

Adapted from Table 12.3.1 – 3 of the Sponsor's CSR for NXL104/1001

Medical Officer comment: The safety and tolerability assessments from this study were supportive of avibactam infusion when given alone in healthy young males with single doses up to 2000 mg, and in combination with ceftazidime, including 2 dose combinations: 250 mg avibactam + 1000 mg ceftazidime and 500 mg avibactam + 2000 mg ceftazidime.

5.3.2 Study NXL104/1002

Primary objective: To investigate the safety and tolerability of avibactam administered alone at 500, 750 and 1000 mg, or in combination (avibactam 500 mg + CAZ 2000 mg) as 30 min intravenous infusion for 5 days (10 days for the subjects receiving the combination (avibactam 500 mg + CAZ 2000 mg) in healthy male volunteers.

Secondary objective: To investigate the pharmacokinetics of avibactam administered alone (single intravenous doses of 50 to 2000 mg) and in combination with ceftazidime (2 doses: 250mg avibactam + 1000mg ceftazidime and 500mg avibactam + 2000mg ceftazidime) in healthy volunteers.

Study dates: 4 September 2007 to 4 December 2007

Study design: A repeated escalating dose study of avibactam alone for 5 days for groups 1 to 3, and of avibactam in combination with ceftazidime for 10 days for group 4 using a randomized, double-blind, placebo-controlled design in healthy young adult male subjects (10 subjects per dose group, 8 active and 2 placebo). The study was divided in two parts.

Part A: consisted of a 21-day screening period, a baseline period (Day -1), followed by a repeated intravenous infusion for 5 days and a completion visit between 2 and 4 days after last dosing. Subjects of group 4 received avibactam in combination with ceftazidime for 10 days. The decision to go to the next dose level was based on safety and tolerability results (AEs reporting, safety laboratory results, local and general tolerability, clinical results) and if possible, pharmacokinetic data from at least 8 out of 10 subjects.

Part B: An open randomized cross-over design in a separate group of 8 healthy volunteers. This part consisted of a 21-day screening period, a baseline period (Day -1), followed by two single administrations of 500 mg of avibactam (either as IV over 30 min or via oral route) separated by a wash-out period of 7 days and a completion visit between 2 and 4 days after last dosing.

Results: Forty-nine (49) subjects were included in this study, 41 in Part A and 8 in Part B. One subject (No.206, dose group 750mg) discontinued from the study after receiving one dose in Part A for personal reasons and was replaced. No subject discontinued from the study in Part B.

Part A: Forty (40) subjects were administered with the planned dose:

- 8 subjects each received 15 doses of placebo (i.e. three times daily for 5 days)
- 24 subjects each received 15 doses of avibactam (500, 750 or 1000 mg)
- 8 subjects each received 30 doses of 500 mg avibactam and 2000 mg CAZ.

No serious or severe adverse events were reported during this study.

In Part A, a total of 5 TEAEs were reported by 5/41 subjects: 1 subject receiving placebo, 1 receiving 750 mg avibactam and 3 receiving 500 mg avibactam + 2000 mg ceftazidime.

One TEAE was reported by 1/8 subjects (No. 105) receiving placebo (12.5%), consisting of moderate infusion site erythema at the morning infusion on Day 3 that resolved spontaneously

One TEAE was reported by 1/8 subjects (No. 209) receiving 750 mg of avibactam (12.5%), consisting of moderate infusion site inflammation at the morning infusion on Day 2 that resolved spontaneously.

Three TEAEs were reported by 3/8 subjects (No. 402, 404 and 406) receiving 500 mg of avibactam + 2000 mg CAZ (37.5%).

- Subject No. 402 presented with mild left ankle pain without other clinical signs (coded to arthralgia) on Day 6, definitely not related to study drug and it resolved spontaneously.
- Subject No. 404 presented with a moderate hematoma at a previous venous puncture site on Day 8 at the morning infusion. The infusion was interrupted, an occlusive dressing was placed on the hematoma, and the infusion site was changed before continuing the infusion. As a result, the infusion ended 15 min later than planned, however the total amount infused (measured electronically by the pump) was as originally planned.
- Subject No. 406 presented with a mild hematoma on Day 11 at the infusion site that resolved spontaneously.

None of the AEs was considered to be related to the study drug by the investigator. No TEAE was reported in subjects receiving 1000 mg of avibactam.

In Part B, no TEAEs were reported, and only one non-TEAE was reported, consisting of left intercostal pain on Day -1 Period 2.

In both parts of the study, values were reported for laboratory parameters but none was considered clinically relevant by the Investigator (> 3× ULN). Among the 9 subjects presenting with abnormal increases in ALT, 1 received placebo (No. 109) and 4 subjects had increases, but they did not reach abnormal (>50 IU/L) ALT values (Subjects No. 101, 205, 404 and 409). For the remaining 4 subjects, increases varied between +34 and +65 IU/L but maximum ALT values were not more than 60 % greater than maximum normal limit (80 IU/L). Detailed profiles of the 9 subjects exhibiting abnormal predefined changes (increase ≥28) are presented in Table 22.

Medical Officer comment: Assessments from this repeat dose escalation study in healthy young males were supportive avibactam infusion alone (up to 1000 mg) and in combination with ceftazidime (avibactam 500 mg + ceftazidime 2000 mg). Although no clinically significant increases were observed, ALT levels exceeded predefined increases from baseline in 4 subjects and should be considered for additional targeted assessment in future studies.

Table 22: Study NXL104/1002 - Individual profiles of subjects exhibiting at least one abnormal predefined change for ALT values

Visit and/or Day	Placebo	500 mg avibactam	750 mg avibactam	500 mg avibactam + 2000 mg CAZ tid					
	Subject No.								
	109	101	205	402	403	404	406	409	410
Screening	20	15	11	19	16	17	17	19	24
Day 1 H0	20	15	10	23	15	15	15	14	17
Day 3 H0	17	17	09	28	12	11	17	12	19
Day 6 H24	30	34	19	38	44*	21	29	27	37
Day 8 H0				42	47*	28	41	35	42
Day 11 H24				57*	80*	46*	53*	50*	63*
End-of-Study	51*	47*	46*	66*	74*	30	46*	35	46
Recheck	35			66*	25				

Adapted from Table 9.3.1 - 3 of the Sponsor's CSR for NXL104/1002 and Appendix 15.2.8.1.3-Part A, * ALT > predefined increase

5.3.3 Study NXL104/1003

Primary objective: To characterize the pharmacokinetics of avibactam administered as a 100 mg single dose over 30 minutes intravenous infusion in normal subjects and patients with varying degrees of renal impairment.

Secondary objective: To investigate the safety and tolerability of avibactam administered as a 100 mg single dose over 30 minutes intravenous infusion in normal subjects and patients with varying degrees of renal impairment.

Study dates: 3 June 2008 to 17 June 2009

Study design: This was a single dose, parallel group, open-label study in subjects with normal renal function and patients with various degrees of renal impairment. Subjects were stratified by different degrees of renal impairment in five groups.

- Group 1: Subjects with normal renal function (creatinine clearance >80 mL/min).
- Group 2: Subjects with mild to moderate renal impairment (creatinine clearance 50 to 79 mL/min).
- Group 3: Subjects with moderate renal impairment (creatinine clearance 30 to 49 mL/min).
- Group 4: Subjects with severe renal impairment (creatinine clearance <30 mL/min) but not requiring hemodialysis or peritoneal dialysis.
- Group 5: Subjects with end-stage renal failure requiring hemodialysis. Subjects participated in two randomized sessions: dialysis session and inter-dialysis session separated by a washout period of 7 to 14 days. All hemodialysed patients had the same duration and same interval of dialysis (4 hours, 3 times a week) and if possible the same

equipment for dialysis with the same blood flow rate (300 to 360 mL/min) and constant dialysate flow (500mL/min during dialysis).

Subjects of Groups 1 to 4 received one single 100 mg IV administration of avibactam. Subjects participated in a 28-day screening period, followed by a baseline period (Day-1, start of hospitalization), followed by single IV dose treatment (D1) and 24 hours post dosing follow-up (hospitalization up to 24h post dosing). An End of Study (EOS) visit was performed 3 to 7 days after dosing.

Hemodialysed subjects (Group 5) participated in two randomly allocated periods separated by a washout period of 7 to 14 days.

Results: 31 subjects (28 men and 3 women) were enrolled and received a single dose of study drug by IV route.

No SAEs were reported during the course of the study.

A total of 19 treatment emergent adverse events (TEAE) were reported in 9 (29%) patients during the course of the study. As presented in Table 23, all events were of mild or moderate intensity and 4 events, reported in 3 patients, were considered possibly related to the study drug. No clinically significant abnormal laboratory value was reported.

Table 23: Study NXL104/1003 - Treatment-Emergent Adverse Events

Renal impaired patients group	Subject #	AE description	Intensity	Investigator Relationship
Healthy subjects		None		
Mild	201	Deterioration of creatinine clearance (Lab)	Mild	Definitely not related
	201	Strange taste in mouth	Mild	Probably not related
	205	Allergic reaction to adhesive	Mild	Definitely not related
	5201	Loose stools	Mild	Probably not related
	5201	Arthritis in left hand	Mild	Probably not related
	5201	Pain in shoulder	Mild	Probably not related
	5201	Knee pain	Mild	Probably not related
Moderate	301	Abdominal pain	Mild	Probably not related
	306	Presyncope	Mild	Definitely not related
	306	Presyncope	Mild	Definitely not related
End stage	502	Tiredness	Mild	Definitely not related
	502	Vomiting	Mild	Definitely not related
	502	Nausea	Mild	Definitely not related
	502	General discomfort	Mild	Possibly related
	503	Stomach pain	Mild	Possibly related
	503	Ructus	Mild	Possibly related
	503	Toothache	Mild	Definitely not related
	504	Staphylococcal infection on fistula	Moderate	Definitely not related
	506	Symptoms of hypoglycemia	Mild	Possibly related

Adapted from Table 2 of the Sponsor's CSR Errata List for NXL104/1003

Patient 502 reported a related TEAE mild discomfort during the wash-out period, at the end of the dialysis session. At the end of study visit, the TEAE was still ongoing with the same intensity and as the patient was lost to follow up no end date for the TEAE was obtained. This patient reported also not related TEAEs neck pain, fatigue, nausea and vomiting, during the wash out period.

Patient 503 reported 2 related TEAEs, mild stomach pain and mild eructation, at the end of dialysis session 04. The TEAEs lasted 2.5 hours and resolved without treatment.

Patient 506 was an insulin-dependent diabetic and reported a related TEAE hypoglycemia at the end of a dialysis session, 5 hours after the second dosing of study drug. This patient self-monitored his blood sugar at 205 mg/dL, 3 hours after dosing, and self-administrated insulin. Two hours later the patient reported tachycardia, shakiness and low blood sugar level (63 mg/mL). The patient drank a beverage with sugar and recovered within approximately 1 hour. The TEAE was reported by the investigator to be study drug related, however the patient self-administration of insulin could also account for the symptoms of hypoglycemia.

Medical Officer comment: Assessments from this single dose study are supportive of avibactam infusion alone at 100mg in subjects with various degrees of renal impairment.

5.3.4 Study NXL104/1004

Primary objective: To characterize the pharmacokinetics of avibactam administered as a 500 mg single dose over 30 minutes IV infusion in young men, elderly men, elderly women, and young women.

Secondary objective: To investigate the safety, tolerability of avibactam administered as a 500 mg single dose over 30 minutes IV infusion in young men, elderly men, elderly women, and young women.

Study dates: 14 February 2008 to 28 October 2008

Study design: This was an open-label study; in which 32 healthy subjects divided in 4 cohorts (8 young male adults, 8 elderly males, 8 elderly females, and 8 young females) were recruited. All subjects received one single 500 mg IV administration of avibactam. Subjects participated in a 28-day screening period, followed by a baseline period (Day-1, start of confinement period), followed by single IV dose treatment (Day 1) and 24 hours post-dose follow-up (confinement up to 24 hours post-dose). An End of Study (EOS) visit was performed 3 to 7 days after dosing. Subjects were contacted by phone 14 days after dosing to assess for the occurrence of adverse events (AEs). Change from baseline shift tables were presented by group and timepoint for laboratory data. Descriptive analysis was presented for selected ECG parameters by group and protocol-specified timepoints for observed values and changes from baseline values. In addition, change from baseline values for ECG QT parameters (QTcB and QTcF) were categorized as ($30 < \Delta QTc < 60$ ms; $\Delta QTc > 60$ ms; $QTc > 450$ ms; $QTc > 500$ ms) and tabulated.

At the request of the FDA, based on pre-clinical toxicology findings (reduced RBC counts in female rats treated with 500 mg/kg/day) direct Coombs testing was added to safety labs.

Safety results: Thirty-two subjects were originally enrolled in the study; subject 101 did not return for the end of study visit and was considered lost to follow-up. A replacement subject 5101 was enrolled. Thirty-two subjects completed the study per protocol. None of the subjects experienced an SAE. Ten subjects (30%) reported at least one TEAE. A total of 18 TEAEs were reported. None of the TEAEs led to a premature discontinuation of the subject from the study. TEAEs that occurred in more than one subject (regardless of relationship to study drug) were application site bruising (4/33; 12%) and headache (2/33; 6%). Three subjects (9%) experienced 6 treatment-emergent adverse events considered to be drug-related, including dry mouth, feeling hot, feeling jittery, dysgeusia, headache, and hyperhidrosis; each event was mild in intensity. A summary of the subjects with drug-related adverse events follows:

- Subject 5101 is a 36 year old black man who experienced a mild headache on Day 1 that resolved within 2 hours without treatment. The headache was considered possibly related to study drug.
- Subject 403 is a 68 year old white female who felt jittery, hot, and experienced hyperhidrosis on Day 1 (~2 hours after the subject was dosed with avibactam). The adverse events resolved within ~15 minutes without treatment. The subject's heart rate and blood pressure remained normal [at 1 hour post-dose, heart rate was 68 bpm (pre-dose 55 bpm) and blood pressure was 90/65 mmHg (pre-dose 101/66 mmHg)]. The adverse events of feeling jittery, feeling hot, and hyperhidrosis were considered possibly related to study drug.
- Subject 407 is a 67 year old white female who experienced dry mouth and dysgeusia on Day 1 that resolved within an hour without treatment. These adverse events were considered possibly related to study drug.

For greater than 20% of the subjects in any cohort, changes in chemistry and hematology parameters from within normal limits to either above or below the normal range included ALT, AST, BUN, chloride, cholesterol, glucose and triglyserides. There were, however, no clinically significant changes in mean chemistry, hematology or urinalysis values at any time after dosing, and none of the TEAEs were related to an abnormal laboratory value.

A direct Coombs test was also performed on Day -1, Day 2 and EOS. Results were negative for all subjects at all time-points.

There were no clinically significant changes in mean BP or HR measured supine or standing over time, and no TEAEs were related to vital signs measurements.

12-Lead ECGs were collected at screening, Day -1 (baseline), and on Day 1 pre-dose, 30 minutes post-dose, 1 hour post-dose, 24 hours post-dose, and at the EOS visit (ranging from Days 3-7). Elderly female subjects had a higher incidence of borderline or prolonged QTc than young subjects. A summary of these subjects are listed as follows:

- Subject 302 is a 66 year old white man that had a QTcF of 456 msec on Day 4; baseline (Day -1) QTcF was 444 msec.
- Subject 404 is a 65 year old white woman that had QTcF values of 464, 455, and 451 msec at 30-min post-dose, 1 hour post-dose, and on Day 6, respectively; baseline (Day -1) QTcF was 452 msec. This subject also had QTcB values of 466, 453, and 457 msec at 30-min post-dose, 1 hour post-dose, and on Day 6, respectively; baseline (Day -1) QTcB was 457 msec.
- Subject 401 is a 67 year old white woman that had a QTcB value of 452 msec at 30- min post-dose; baseline (Day -1) QTcB was 454 msec.
- Subject 204, a 25 year old white female, had a Day 1 pre-dose QTcB of 405 msec and a HR of 55 bpm. QTcB of 448 msec was noted on Day 1 at 30-min post-dose with no other ECG abnormalities and a HR of 82 bpm. The QTcF at these times was noted to be 415 and 426 msec, respectively.
- Subject 207, a 23 year old white female, had a Day 1 pre-dose QTcB of376 msec and a HR of 78 bpm. QTcB of 406 msec was noted on Day 6 with no other ECG abnormalities and a HR of 75 bpm. The QTcF at these times was noted to be 375 and 395 msec, respectively.

Medical Officer comment: No subjects experienced any TEAEs related to an abnormal laboratory value or any clinically significant change from baseline laboratory or vital sign observations. Assessments from this single dose study are supportive of a single 500mg avibactam infusion in young men, young women, elderly men and elderly women alone. This study was also reviewed by the Interdisciplinary Review Team. The overall assessment was that no significant QTc prolongation effects of CAZ-AVI were detected. Please also refer to their review submitted to IND-101307, dated 19 Jun 2012.

5.3.5 Study D4280C00007

Primary objective: To investigate the effect of supratherapeutic doses of CAZ-AVI or ceftaroline-avibactam (CXL-AVI) on the QT interval.

Secondary objectives:

- To investigate the effect of CAZ-AVI and CXL-AVI, on additional electrocardiogram variables
- To assess the pharmacokinetics of avibactam, ceftaroline, ceftazidime and moxifloxacin
- To evaluate the safety and tolerability of CAZ-AVI and CXL-AVI.
- To explore the relationship between avibactam and ceftazidime plasma concentrations and the QT interval.

Study dates: 11 February 2011 to 24 May 2011

Study design: This was a double-blind, randomized, placebo-controlled, 4-period crossover study in 51 healthy male subjects evaluating single delivered doses of CAZ-AVI (3000/2000 mg) and CXL-AVI (1500/2000 mg), compared with placebo and a single, open-label 400 mg oral dose of moxifloxacin as a positive control for assay sensitivity. The study comprised 6 visits with an approximate total duration of 9 weeks.

Each eligible subject was randomized to 1 of 4 treatment sequences in the morning of Day 1 of each treatment visit (Visits 2 to 5) in a crossover manner utilizing a William's design (e.g., using the sequences of ABDC, BCAD, CDBA, and DACB).

- Treatment A: CXL-AVI (2000 mg avibactam + 1500 mg ceftaroline IV)
- Treatment B: CAZ-AVI (2000 mg avibactam + 3000 mg ceftazidime IV)
- Treatment C: Moxifloxacin 400 mg (1 oral tablet)
- Treatment D: Placebo infusion (saline IV)

Between each treatment there was a washout period of at least 3 days from the last administration received until the following administration (dose to dose).

Results: Eight subjects prematurely discontinued administration of the investigational product due to: AEs (4 subjects; the first 3 events were reported after CXL-AVI treatment, while the fourth event was reported after receiving CAZ-AVI), severe non-compliance to the protocol (2 subjects), while 2 subjects withdrew consent.

At least one AE was reported for 27 subjects (54.0%) after CXL-AVI, 14 subjects (30.4%) after CAZ-AVI, 8 subjects (17.4%) after moxifloxacin and 8 subjects (17.0%) after placebo. Most of the events were considered to be causally related to the investigational product administration by the Investigator and the majority of the events resolved.

The most frequently reported AE was nausea in the SOC Gastrointestinal disorders. Most of these events were reported after CXL-AVI:

• 16 subjects (32.0%) after CXL-AVI treatment, in all except 2 subjects the nausea was considered to be mild and in all except 1 subject it was considered to be causally related to the investigational product administration by the Investigator

• 1 subject (2.2%) after CAZ-AVI treatment, and considered to be mild and causally related to the investigational product administration by the Investigator

The events were reported during the infusion. No nausea events were reported for subjects who received moxifloxacin or placebo.

Most of the AEs were considered to be causally related to the investigational product after CXL-AVI and CAZ-AVI treatment, and included dyspepsia, nausea, vomiting, urticaria, retching, catheter site pain, chills, decreased appetite, headache, dysuria, pruritus, erythematous rash and pruritic rash.

The majority of the AEs were considered to be mild by the Investigator and no severe events were reported. Moderate events were nausea, blood creatine phosphokinase increased, toothache and urticaria, all after CXL-AVI treatment, and urticaria after CAZ-AVI treatment.

Adverse events observed by Preferred Term (PT) arranged by SOC are presented in Table 24.

Table 24: Study D4280C00007 - Number (%) of Subjects who had at least One Adverse Event by Preferred Term, arranged by System Organ Class (Safety analysis set)

Adverse event category	Statistic	CXL-AVI 1500/2000 N=50	CAZ-AVI 3000/2000 N=46	Placebo N=47	Moxifloxacin 400 mg N=46
Number of subjects with adverse events	n (%)	27 (54.0)	14 (30.4)	8 (17.0)	8 (17.4)
Cardiac disorders	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Palpitations	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Eye disorders	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Episcleritis	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	n (%)	17 (34.0)	3 (6.5)	0 (0.0)	2 (4.3)
Constipation	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Diarrhea	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Dyspepsia	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Nausea	n (%)	16 (32.0)	1 (2.2)	0 (0.0)	0 (0.0)
Retching	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Toothache	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	n (%)	2 (4.0)	1 (2.2)	0 (0.0)	0 (0.0)
General disorders and administration site	n (%)	6 (12.0)	3 (6.5)	5 (10.6)	3 (6.5)
Application site irritation	n (%)	2 (4.0)	1 (2.2)	1 (2.1)	2 (4.3)
Catheter site pain	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.2)
Catheter site phlebitis	n (%)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)
Chills	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema peripheral	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Vessel puncture site hemorrhage	n (%)	1 (2.0)	2 (4.3)	3 (6.4)	0 (0.0)
Vessel puncture site	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Infections and infestations	n (%)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	n (%)	2 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	n (%)	2 (4.0)	0 (0.0)	1 (2.2)	0 (0.0)
Excoriation	n (%)	1 (2.0)	0 (0.0)	1 (2.2)	0 (0.0)
Skin laceration	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse event category	Statistic	CXL-AVI 1500/2000 N=50	CAZ-AVI 3000/2000 N=46	Placebo N=47	Moxifloxacin 400 mg N=46
Blood creatine phosphokinase increased	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	2 (4.3)
Back pain	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Myalgia	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Pain in extremity	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Nervous system disorders	n (%)	5 (10.0)	2 (4.3)	1 (2.1)	2 (4.3)
Headache	n (%)	3 (6.0)	1 (2.2)	0 (0.0)	2 (4.3)
Hypoesthesia	n (%)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)
Sleep paralysis	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	n (%)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)
Renal and urinary disorders	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Dysuria	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal congestion	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	n (%)	5 (10.0)	4 (8.7)	2 (4.3)	1 (2.2)
Dermatitis allergic	n (%)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)
Dermatitis contact	n (%)	0 (0.0)	1 (2.2)	1 (2.1)	0 (0.0)
Erythema	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)
Petechiae	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Rash erythematous	n (%)	1 (2.0)	1 (2.2)	0 (0.0)	0 (0.0)
Rash pruritic	n (%)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urticaria	n (%)	2 (4.0)	1 (2.2)	0 (0.0)	0 (0.0)

Adapted from Table 11, D4280C00007 CSR. A subject can have 1 or more Preferred Terms reported under a given System Organ Class. Adverse events occurring during the washout period between treatments were attributed to the last treatment received.

Four subjects prematurely discontinued from the study due to AEs:

CXL-AVI 1500/2000 mg—Pruritic rash

Subject E0001007, a 32-year-old Black or African American male, receiving an infusion of CXL-AVI, experienced a pruritic rash on his neck of mild intensity 10 minutes after the start of the infusion on Day 2, 04 March 2011, of Period 1. The infusion was not interrupted, and the event resolved after 1.3 hours. The subject did not receive any concomitant medication for the

treatment of the event. The event was assessed as causally related to the investigational product administration by the Investigator, and led to the discontinuation of the investigational product as well as the premature withdrawal of the subject from the study.

CXL-AVI 1500/2000 mg—Urticaria
Subject E0001019, a 30-year-old Black or African American male, receiving an infusion of CXL-AVI, experienced a localized urticaria lesion on his neck of mild intensity 30 minutes after the start of the infusion on Day 2, 23 March 2011, of Period 3. The infusion was not interrupted, and the event resolved after 1.1 hours. A cold pack was administered. The event was assessed as causally related to the investigational product administration by the Investigator, and led to the discontinuation of the investigational product as well as the premature withdrawal of the subject from the study.

CXL-AVI 1500/2000 mg—Urticaria
Subject E0001038, a 26-year-old White male, receiving an infusion of CXL-AVI, experienced urticaria of moderate intensity 32 minutes after the start of the infusion on Day 2, 05 April 2011, of Period 1. The infusion was discontinued early, and the event resolved after 1.5 hours. The subject received 50 mg diphenhydramine intravenously once for the treatment of the event. The event was assessed as causally related to the investigational product administration by the Investigator, and led to the discontinuation of the investigational product as well as the premature withdrawal of the subject from the study.

CAZ-AVI 3000/2000 mg—Urticaria
Subject E0001082, a 21-year-old Black or African American male, receiving an infusion of CAZ-AVI, experienced urticaria of mild intensity 37 minutes after the start of the infusion on Day 5, 17 May 2011, of Period 4. The infusion was discontinued early, and the event resolved after 1.6 hours. The subject received 50 mg diphenhydramine intravenously once for the treatment of the event. The event was assessed as causally related to the investigational product administration by the Investigator, and led to the discontinuation of the investigational product as well as the premature withdrawal of the subject from the study.

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 25: 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.

Medical Officer comment: Premature withdrawals due to urticaria were the most significant safety findings; however, three out of the four subjects withdrawn had received ceftaroline-avibactam, not ceftazidime-avibactam, and attribution to either component or avibactam in particular is uncertain for each case.

With regard to the QT analysis, assay sensitivity was established in subjects given moxifloxacin. Measures of analysis (i.e. least square mean differences between CAZ-AVI in QTcF, maximal QTcF interval or interval increase, as well as the upper bound of the 2-sided 90% CI) revealed no significant QT/QTc prolongation concerns following a single supratherapeutic dose(3000/2000 mg) of CAZ-AVI.

5.3.6 Study D4280C00008

Primary objectives:

1. To determine the mass balance after a single IV dose of [^{14}C]-avibactam
2. To determine the routes of [^{14}C]-avibactam metabolism and excretion
3. To estimate the whole blood and plasma partitioning of total radioactivity
4. To determine the urine and fecal recovery of radioactivity

Secondary objectives:

1. To assess the IV pharmacokinetics of [^{14}C]-avibactam
2. To identify and characterize the metabolites of [^{14}C]-avibactam in plasma, whole blood, urine and feces
3. To provide additional safety and tolerability information for avibactam

Study dates: 17 October 2011 to 10 November 2011

Study design: Study D4280C00008 was an open-label single-dose study in 6 healthy male subjects designed to assess the distribution, metabolism and excretion following administration of approximately 500 mg [^{14}C]-avibactam.

All healthy volunteers, at ages of 36 to 63 years, were recruited to the study at a single clinic in the UK and received a single IV infusion administration containing 500 mg avibactam in 100 mL of saline over 60 min and a target dose of radioactivity of no more than 300 µCi (11.1 MBq) [^{14}C]-avibactam in a fasted state. This dose of radioactivity was chosen to minimize the radiation dose, while providing sufficient [^{14}C] in blood, plasma, urine and feces, to allow quantification of compound related material.

Safety results: Five volunteers were white and one volunteer was English/Caribbean.

One healthy volunteer (Subject E0001983) reported a mild AE (headache) after dosing with [^{14}C]-avibactam approximately 4 days following discharge from the clinical unit. The volunteer took paracetamol for the headache, and it resolved within 2 hours of onset.

No other AEs were reported after dosing with [^{14}C]-avibactam. All mean hematology and clinical chemistry values were within the normal reference range at admission and discharge, and there were no notable mean changes from baseline for any parameter. There were no clinically significant findings from physical exam or from any vital signs or ECG parameters.

Medical Officer comment: In this study with a single dose of approximately 500 mg [^{14}C]-avibactam given to healthy male volunteers, no significant safety findings were reported.

5.3.7 Study D4280C00009

Primary objectives: To measure and compare the concentration of ceftazidime and avibactam in bronchial epithelial lining fluid (ELF) and plasma, following administration of at least 2 different dosing regimens in healthy subjects (volunteers).

Secondary objectives: To assess the safety and tolerability of ceftazidime and avibactam when administered every 8 hours for 3 days via a 2-hour infusion (Cohorts A and B) or a 4-hour infusion (optional Cohort C).

Exploratory objectives: To correlate the plasma and ELF concentration-time courses by a population PK modelling approach.

Dates: 5 September 2011 to 27 July 2012

Design: Study D4280C00009 was an open-label, two-part study in healthy male subjects to assess the concentration of CAZ-AVI in bronchial ELF and plasma following administration of 2 different dosing regimens in healthy subjects. The study was divided in 2 parts: Part 1 (procedural pilot including 2 subjects) was performed without investigational product (IP) administration to verify optimal execution of the procedures and acquisition of satisfactory samples (main part with IP administration including 43 subjects). Two subjects were entered in pilot Part 1 and did not receive any IP. In Part 2, penetration of ceftazidime and avibactam in

the ELF was observed following 2-hour IV administration of CAZ-AVI at 2000/500 mg or 3000/1000 mg, every 8 hours for 3 days. Part 2 of the study was further divided in Cohorts A and B. Based on adequate ELF penetration from data in the first two cohorts it was decided not to continue with the optional Cohort C. For both cohorts, subjects received 1 dose of the IP every 8 hours for 3 days (total 9 doses).

In total, 43 healthy male subjects were randomized to receive either:

- Cohort A (22 subjects) – ceftazidime 2000 mg + avibactam 500 mg infused (IV) over 2 hours or
- Cohort B (21 subjects) – ceftazidime 3000 mg + avibactam 1000 mg infused (IV) over 2 hours

For both of these cohorts, bronchoscopy with BAL was performed once on each subject after the last dose from the start of infusion at one of the following time points: 2, 4, 6 and 8 hours. There were approximately 5 subjects per BAL time point.

Safety Results: 42 subjects completed the study. One subject in Cohort B was withdrawn due to an important protocol deviation (leakage at 3-way tap connection during his third infusion), but was included in the safety analysis set. All subjects were males. Mean age was 25 years. In Part 2, 83.7% were white.

No deaths, SAEs or severe AEs were reported during the study and no subjects discontinued CAZ-AVI due to an AE. The number of healthy subjects with at least one AE was similar (15 [68.2%] subjects) in Cohort A and (12 [57.1%] subjects) in Cohort B. The most frequently reported AEs were headache (reported in 10 [23.3%] subjects, overall), influenza like illness and abnormal urine odor (each reported in 4 [9.3%] subjects, overall). In Cohort A, 3 (13.6%) subjects had headache that was considered by the Investigator to be related to the IP. All of the AEs of abnormal urine odor were considered to be related to the IP by the Investigator.

None of the laboratory values above or below the laboratory reference ranges inclusive of the elevated liver function test results were considered to be of clinical significance by the Investigator. There were transient elevations of liver enzymes as summarized in Table 26. There were no clinically significant abnormalities in laboratory values, vital signs, physical examination or ECG findings.

Medical Officer comment: The observations of transient elevation of liver enzymes in this study were not clinically significant and do not appear to be consistent with liver injury. This was also previously noted in other studies with CAZ-AVI, but the relation, if any, to the addition of avibactam is unclear. Minor elevations in serum aminotransferase and alkaline phosphatase values, which are generally transient and not associated with symptoms or development of more severe liver injury, have previously been described with cephalosporins, including ceftazidime. Evaluation of liver enzyme elevations and hepatotoxicity, however, should be considered a safety concern of particular importance in future study.

Table 26: Study D4280C00009 - Elevated Liver Enzyme Values

Part/cohort	Subject	Study day	Elevated value
Alanine aminotransferase			
Part 2/A	E0001042	Follow-up	79 U/L
Part 2/B	E0001120	Follow-up	75 U/L
	E0001128	Day 4	58 U/L
Aspartate aminotransferase			
Part 2/A	E0001016	Day 4	48 U/L
	E0001032	Day 4	71 U/L
Part 2/B	E0001088	Follow-up	44 U/L
Alkaline phosphatase			
Part 1	E0001002	Screening	126 U/L
		Day -1	123 U/L
		Follow-up	110 U/L
Total bilirubin			
Part 2/A	E0001016	Day 4	22.1 µmol/L
	E0001028	Day 5	23 µmol/L
	E0001032	Day 4	36 µmol/L
	E0001035	Day 5	21.9 µmol/L
	E0001148	Screening	22.2 µmol/L
Part 2/B	E0001088	Screening	21.4 µmol/L
		Follow-up	20.8 µmol/L
	E0001096	Day 5	22 µmol/L
	E0001103	Screening	21.7 µmol/L
		Day 4	23.2 µmol/L
		Day 5	26.8 µmol/L
		Follow-up	31.8 µmol/L
	E0001136	Screening	25.2 µmol/L
		Follow-up	31.8 µmol/L

Source: Table 15 - D4280C00009 CSR
Normal ranges of laboratory values for male subjects aged 18 to 50 years:

- Alanine aminotransferase: 11 to 57 U/L
- Aspartate aminotransferase: 3 to 42 U/L
- Alkaline phosphatase: 42 to 100 U/L
- Total Bilirubin: 1.7 to 20.7 µmol/L.

5.3.8 Study D4280C00010

Primary objective:
• To investigate the safety and tolerability of avibactam alone or in combination with ceftazidime administered as single and repeated IV infusions in healthy Japanese subjects.

Secondary objectives:
• To investigate the PK of avibactam alone or in combination with ceftazidime.
• To investigate the influence of avibactam alone or in combination with ceftazidime on intestinal bacterial flora in healthy Japanese subjects.

Dates: 17 February 2011 to 08 April 2011

Design: This was a randomized, double-blind, placebo-controlled study of avibactam alone and in combination with ceftazidime administered as single and repeated IV doses in 16 healthy Japanese volunteers (aged 20 to 45 years). Subjects received a single IV administration of 500 mg avibactam alone, avibactam in combination with ceftazidime (500/2000 mg), or placebo on Day 1. Repeated dosing started on Day 3 with avibactam alone, avibactam in combination with ceftazidime, or placebo administered every 8 hours for 4 days (Day 3 to Day 6) and a final single dose on Day 7.

Safety results: A total of 16 healthy male Japanese subjects were enrolled, and all 16 subjects were randomized to receive either avibactam (N = 6), CAZ-AVI (N = 7) or placebo (N = 3). All study drugs were administered by IV infusion at a constant rate over 120 minutes. All but one subject (randomized to CAZ-AVI) completed the study. Subject E0001016 withdrew from the study for personal reasons. This subject was included in the safety analysis and PK analysis up to the point at which he discontinued.

There were no AEs with an outcome of death, SAEs, AEs that led to withdrawal from the study, or other significant AEs during the single dose period. One AE of orthostatic tachycardia was experienced by a single subject in the avibactam treatment group during the single dose period of the study. The event, which was considered mild in severity and related to the study drug, started approximately 8 hours after the start of dosing on Day 1 and resolved spontaneously by Day 10.

Three subjects experienced a total of eight AEs during the multiple-dose period. All were considered mild in severity, and all but one AE of contact dermatitis were considered related to the study drug.

Two subjects (33.3%) who received avibactam alone experienced a total of seven AEs, including transaminases increased, infusion site extravasation, infusion site thrombosis, chest discomfort, dyspnea, and palpitations. The AE of chest discomfort was not associated with an abnormal

ECG or significant vital signs changes. One subject (14.3%) who received CAZ-AV I experienced a single AE of orthostatic hypotension.

No deaths, SAEs, or AEs leading to discontinuation from the study occurred during the multiple dose period of the study.

One subject (Subject E0001018 randomized to avibactam alone), who was a 41 year-old Japanese male with no history of hepatitis, liver conditions/disease, drug allergies/reactions, and negative serology on screening and admission, exhibited elevated transaminases (alanine aminotransferase [ALT] 339 to 522 u/l [reference range; 17 to 63 u/l], aspartate aminotransferase [AST] 165 to 246 u/l [reference range; 15 to 41 u/l], gamma glutamyl-transpeptidase [GGT] 107 to 154 u/l [reference range; 7 to 50 u/l]) on Day 5, Day 7, and Day 8 of the study. The subject's alkaline phosphatase (ALP) was 133 to 169 u/l [reference range; 38 to 126 u/l] on Day 5 to Day 8, and total bilirubin was 0.7 mg/dl [reference range; 0.2 to 1.2 mg/dl] on Day 5 and Day 8. At the scheduled Follow-up Visit (3 days after the last dose of study drug), the subject’s transaminase levels had trended lower but were not yet normalized (ALT 307 u/l, AST 86 u/l, GGT 145 u/l). The subject's ALP was 171 u/l, and total bilirubin was 0.6 mg/dl.

The subject was not symptomatic (e.g., no nausea, vomiting, abdominal pain or tenderness, anorexia, or change in bowel patterns, etc.) during the time period the liver function tests were abnormal, and he did not take concomitant medications during the study. All other laboratory test results for this subject were within clinically acceptable limits. The subject did not return to the clinical unit for further evaluations and was considered lost to follow-up. The transaminases increase was considered mild in severity and related to the study drug.

No other clinically significant individual chemistry, hematology or urinalysis laboratory values were identified for any of the subjects.

Mean chemistry and hematology laboratory values occasionally fell slightly outside of the reference ranges but remained within acceptable limits during the study. Increases in mean ALT, AST, and GGT values were seen for the avibactam group beginning on Day 5 and were attributable to values measured in a single subject. No other differences in mean chemistry and hematology values were identified across treatment groups over time.

Variations in mean supine and standing vital signs were similar across the treatment groups. Two subjects (one subject in the avibactam treatment group and one subject in the CAZ-AVI treatment group) experienced a total of three AEs related to vital signs including orthostatic tachycardia, palpitations, and orthostatic hypotension. All events were considered mild in severity and resolved spontaneously by the end of the study.

None of the subjects experienced clinically significant abnormalities in resting ECG data at any time point. There were no AEs related to ECG measurements. A summary of mean change from

baseline values for ECG parameters (RR, PR, QRS, QT, and QTcF) showed comparable values for all treatments. There were no clinically relevant changes over time. None of the subjects had a QTcF greater than 450 ms or a change from baseline > 30 ms. There were no clinically significant findings on physical examinations.

Medical Officer comment: The observations of transient elevation of serum aminotransferase and alkaline phosphatase have also been previously noted in other studies with CAZ-AVI (the association with addition of avibactam has been unclear), but minor elevations in ALT, 47 and 46 IU/L, were reported in healthy two volunteers who had been given multiple doses of avibactam alone at 500 mg and 750 mg, respectively. Mean values for this study appear to be driven by one patient, indicating that this was likely an idiosyncratic event. Although AST and ALT levels reached were greater than five times the upper limit of normal, there was no association with elevated bilirubin or alkaline phosphatase meeting Hy's criteria, associated symptoms and levels appeared to trend downward after the study drug was stopped. Unfortunately, the subject was lost to follow up. Nevertheless, given the temporal association and trend upon dechallenge, causality due to avibactam is likely.

5.3.9 Study D4280C00011

Primary objectives:
• Part A: to investigate the single- and multiple-dose PK of avibactam and ceftazidime following a single administration of CAZ-AVI on Days 1 and 11 and multiple administrations every 8 hours from Day 2 to Day 10
• Part B: to investigate the effect on the PK of co-administering CAZ-AVI compared to administration of the individual components (ceftazidime and avibactam alone)

Secondary objective:
• To assess safety and tolerability of avibactam, ceftazidime, and CAZ-AVI when administered as a 2-hour infusion every 8 hours

Study dates: 11 October 2011 to 17 October 2012

Study design: This was a two-part study to investigate safety and PK of avibactam and ceftazidime following a single 2-hour infusion of CAZ-AVI and in multiple doses every 8 hours for up to 9 days in healthy volunteers.

Part A was an open-label, single-treatment study in which approximately 16 healthy male volunteers were enrolled. The investigational product was administered as a 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime once on the morning of Day 1 and every 8 hours from Day 2 to Day 10 (inclusive) (3 infusions per day). The healthy volunteers received a single infusion on Day 11. Serial blood samples for PK assessments were collected

Part B was an open-label, randomized, 3-way cross-over study in which approximately

27 healthy male were enrolled. The healthy volunteers were randomized to 3 treatment sequences and all healthy volunteers received all 3 treatments (Treatment A, Treatment B, and Treatment C). Treatment A was a 2-hour infusion of 500 mg avibactam, Treatment B was a 2-hour infusion of 2000 mg ceftazidime, and Treatment C was a 2-hour infusion of 500 mg avibactam and 2000 mg ceftazidime (CAZ-AVI). In each cross-over period (Period 1, Period 2, and Period 3) the healthy volunteers received a single infusion on the morning of Day 1 and every 8 hours from Day 2 to Day 3 (inclusive) (3 infusions per day). The healthy volunteers received a single infusion on Day 4. Serial blood and urine samples for PK assessments were collected on Day 1 and Day 4 of each treatment period. The treatment periods was separated by a wash-out period of at least 2 days.

Safety results: A total of 92 healthy volunteers were screened and 43 healthy volunteers (16 healthy volunteers in Part A and 27 healthy volunteers in Part B) were randomized and completed this study. All healthy volunteers were male (no female healthy volunteers were screened).

The study was temporarily halted due to original preset study stopping criteria based on liver chemistries. At the time of the halt, 8 healthy volunteers had been recruited to Part A of the study. Following evaluation of the data, the protocol was amended with intensified monitoring and individual withdrawal criteria and the study was restarted.

One ongoing medical history item of idiopathic angioedema was reported by Volunteer E0002060 in Part B. The healthy volunteer only revealed this medical history after he experienced an episode of angioedema and sought medical help. He had denied any past medical history at screening.

No deaths, SAEs, or discontinuation of the investigational product administration due to AEs were reported.

Overall, at least 1 AE was reported for 25 of 43 (overall) healthy volunteers (58.1%): 9 of 16 healthy volunteers (56.3%) in Part A and 16 of 27 healthy volunteers (59.3%) in Part B. The proportion of healthy volunteers with at least 1 AE was similar between the 2 parts. The most frequently reported AE was abnormal urine odor, which occurred in 8 (18.6%) volunteers.

All 8 healthy volunteers had received the protocol-specified 29 infusions of CAZ-AVI over 11 days. No healthy volunteers had ALT ≥3×ULN or AST ≥3xULN and total bilirubin ≥2×ULN; however, two of the 8 healthy volunteers were reported to have ALT levels above 2×ULN (2.5×ULN and 2.6×ULN, respectively and max ALT elevation was 146 U/L on Day 11, 288 h post-dose) at the end of the investigational product administration and therefore according to preset study protocol criteria the study was halted based on laboratory findings. Four additional healthy volunteers had elevations in ALT that did not fulfil the study stopping criteria (the highest rise was 1.7×ULN). Neither bilirubin nor alkaline phosphatase was elevated in any healthy volunteer and no clinical symptoms attributable to hepatic disorder were observed.

Furthermore no hepatic AEs or SAEs were reported in the study. All healthy volunteers had follow-up visits and laboratories and, in all healthy volunteers but one, the ALT values decreased to within normal limits by 12 days after the last administration of the investigational product. The one exception was a healthy volunteer whose ALT was trending down but remained slightly above normal 7 days after the last infusion. No healthy volunteers experienced clinical symptoms related to the liver in the follow-up period.

Medical Officer comment: Mild, reversible transaminase elevations reported here resulted in the study being temporarily halted due to pre-specified stopping rules. As consistent with the profile for ceftazidime and with prior studies with CAZ-AVI and avibactam alone, transient elevations have been previously been described. In this study, no associated elevations reaching threshold for Hy's Law were reported.

5.3.10 Study D4280C00012

Primary objectives: To investigate the effect on the PK of ceftazidime, avibactam and metronidazole when administering CAZ-AVI plus metronidazole in combination compared to administration of the individual components (CAZ-AVI and metronidazole).

Secondary objectives: To assess safety and tolerability of CAZ-AVI and metronidazole when administered as a 2- and 1-hour infusion, respectively, every 8 hours.

Study dates: 17 February 2012 to 2 July 2012

Study design: This was an open-label, three-way crossover, PK and drug-drug interaction study of CAZ-AVI and metronidazole when administered alone and in combination in healthy volunteers. Each volunteer received 3 treatments (Treatments A, B, and C).

Treatment A: CAZ-AVI (2000/500 mg) single infusion Day 1, followed by every 8 hours for a total of 8 infusions.

Treatment B: metronidazole (500 mg): single infusion Day 1, followed by every 8 hours for a total of 8 infusions.

Treatment C: metronidazole followed by CAZ-AVI (single infusion of each investigational product Day 1), then every 8 hours for a total of 16 infusions (8 infusions of each investigational product). The intravenous line was flushed with saline solution between administrations of metronidazole and CAZ-AVI.

Any healthy volunteer who met the individual withdrawal criteria (Table 27) was to be withdrawn from the study and advised to continue assessments to ensure his/her safety.

Table 27: Study D4280C00012 - Individual healthy volunteer discontinuation and intensified monitoring criteria

Liver chemistry variable	Intensified monitoring criteria	Individual healthy volunteer withdrawal criteria
ALT	Level >2× ULN, monitor at least every 48 hours until return to within the normal limits or stable, as judged by the investigator	Level >3× ULN
ALP	Increase by >100%, check GGT, monitor at least every 48 hours until return to within the normal limits or stable, as judged by the investigator.	>2× ULN
Bilirubin	>1.5× ULN, monitor at least every 48 hours until return to within the normal limits or stable as judged by the investigator.	>2× ULN

Safety results: A total of 118 healthy volunteers were enrolled (signed informed consent) of which 28 healthy volunteers were randomized and received treatment in this study. All volunteers were male. One healthy volunteer, Volunteer E0001048, withdrew consent prior to investigational product administration in Period 3 (Treatment B) due to multiple unsuccessful attempts to start his blood draw intravenous catheter. The healthy volunteer was withdrawn from the study after completing Period 1 (Treatment C) and Period 2 (Treatment A). A total of 27 healthy volunteers received all 3 treatments and completed the study.

No deaths or SAEs were reported and no healthy volunteers discontinued the investigational product due to an AE.

The highest number of healthy volunteers reported AEs after Treatment C (15 healthy volunteers [53.6%]). For Treatments A and B, the AE reported for the highest number of healthy volunteers was contact dermatitis (ECG patch irritation). For Treatment C, the AEs reported for the highest number of healthy volunteers were headache, diarrhea and contact dermatitis (ECG patch irritation).

No healthy volunteers had ALT ≥3× ULN or aspartate aminotransferase (AST) ≥3× ULN, and total bilirubin ≥2 × ULN.

Medical Officer comment: The doses studied in combination with metronidazole were the same doses being developed for treatment of cIAI. No additional/significant safety issues or drug-drug interactions were identified.

5.3.11 Study CXL-PK-01

Part A objectives: To evaluate the safety, tolerability, and pharmacokinetics of ceftaroline and avibactam following co-administration of a single IV dose of ceftaroline fosamil (the prodrug of ceftaroline) and avibactam in healthy subjects.

Part B objectives: To evaluate the safety, tolerability, and pharmacokinetics of ceftaroline and avibactam following co-administration of multiple IV doses of ceftaroline fosamil and avibactam over 10 days to healthy subjects.

Study dates: 21 July 2009 to 26 October 2009

Study design: This was a single-center, two-part randomized study in 60 healthy subjects conducted as part of the ceftaroline-avibactam development program. Part A was an open-label, three-way crossover, single-dose study in which 12 subjects received 3 treatments (single dose of ceftaroline 600 mg, avibactam 600 mg or ceftaroline and avibactam 600/600 mg) in a randomized manner separated by a 5-day washout period. Part B was a randomized, double-blind, placebo-controlled, 10-day, multiple-dose study in which subjects received 1 of 4 dose combinations of ceftaroline and avibactam or placebo.

Part A:
A total of 12 subjects received each of the following treatments in a randomized order separated by a 5-day washout period:
Treatment A: single dose of 600 mg ceftaroline fosamil via IV infusion over 60 minutes
Treatment B: single dose of 600 mg avibactam via IV infusion over 60 minutes
Treatment C: single dose of 600 mg ceftaroline fosamil and 600 mg avibactam via IV infusion over 60 minutes

Part B:
A total of 48 subjects were randomized to 1 of the following 4 cohorts (9 active, 3 placebo per cohort):
Cohort 1: 600 mg ceftaroline fosamil and 600 mg avibactam, or placebo, every 12 hours (q12h) for 10 days via IV infusion over 60 minutes
Cohort 2: 400 mg ceftaroline fosamil and 400 mg avibactam, or placebo, every 8 hours (q8h) for 10 days via IV infusion over 60 minutes
Cohort 3: 900 mg ceftaroline fosamil and 900 mg avibactam, or placebo, q12h for 10 days via IV infusion over 60 minutes
Cohort 4: 600 mg ceftaroline fosamil and 600 mg avibactam, or placebo, q8h for 10 days via IV infusion over 60 minutes

Safety results: No subjects died or experienced an SAE. There were no discontinuations due to TEAEs in Part A (single dose administration).

Two of 36 (5.6%) subjects who received study drug in Part B withdrew from the study because of TEAEs. Subject 1008 (a 40-year-old white woman) in Treatment Group I experienced an TEAE of a generalized rash on Day 8 and was discontinued from study drug after the Day 9 morning dose. This TEAE was mild in severity, and the subject received analgesics. The rash improved significantly within the first 24-48 hours after study drug discontinuation, and resolved 6 days after the last dose. Subject 4013 (a 34 year old white male) in Treatment Group IV experienced

TEAEs of generalized rash and pruritus, diaphoresis, fever, and tachycardia on Day 9 and was discontinued from study drug. The subject received antipyretics and antihistamines, and the fever, diaphoresis, and tachycardia resolved within approximately 15 hours, with significant improvement of the pruritus and rash within 24-48 hours and resolution in approximately 4 days.

A total of 12 TEAEs were reported by 7 (58.3%) subjects during the study in Part A and headache was the most frequently reported TEAE.

A total of 307 TEAEs were reported by 46 subjects (95.8%) in Part B, with 252 TEAEs reported among 34 of 36 (94.4%) subjects assigned to study drug, and 55 TEAEs reported among 12 of 12 (100%) subjects assigned to placebo. The most frequent TEAEs were mild infusion site reactions reported in 34 of 36 (94.4%) subjects who received study drug, and in 9 of 12 (75%) subjects who received placebo.

In Part A, three subjects had potentially clinically significant (PCS) changes in clinical laboratory evaluations at EOS, compared with those evaluations at screening. Two subjects had low glucose 4 days following treatment, and one subject had low protein. In Part B, ten subjects had PCS post-baseline clinical laboratory abnormalities, 9 of 36 (25%) subjects in study drug groups, and 1 of 12 (0.8%) subjects in placebo groups. One PCS low absolute neutrophil count reported as a TEAE.

No subjects in Part A had PCS abnormal vital signs. Ten subjects in Part B had PCS abnormal vital signs, 6 of 36 (16.7%) subjects in study drug groups, and 4 of 12 (33%) subjects in placebo groups. None of the PCS abnormal vital signs were reported as a TEAE.

No abnormal ECG measurements and no ECG changes from screening were considered clinically significant in Part A and Part B of the study.

Medical Officer comment: Premature withdrawals due to rash/pruritus were the most significant safety findings similar to the AEs (e.g. urticaria) reported in Study D4280C00007. The subjects withdrawn had received ceftaroline-avibactam, not ceftazidime-avibactam, and attribution to either component or avibactam in particular is uncertain for each case.

6 Review of Efficacy

Efficacy Summary

For this 505(b)(2) application, evaluation of efficacy relies on the previous finding of efficacy for ceftazidime using prescribing information as described in the Fortaz label and historical evidence as described in published literature. Avibactam is an NCE that demonstrates a contributory effect only when given in combination with a β-lactam (such as ceftazidime) for the treatment of certain β-lactamase-producing pathogens. Support for the contribution of the avibactam in the combination with ceftazidime was drawn from non-clinical studies, as previously discussed in Section 4, as well as from descriptive clinical trial data, particularly for subjects with infections due to CAZ-NS pathogens. Inference testing is therefore relatively limited compared to what might otherwise be expected in a 505(b)(1) application.

The Applicant submitted results of two Phase 2 trials, one each in cUTI (NXL104/2001, or Trial 2001) and cIAI (NXL104/2002, or Trial 2002). Neither of the two Phase 2 trials were designed with formal pre-specified hypotheses or powered for any statistical inference testing (statistical analyses are based only on descriptive data summaries), but the results provided important conclusions leading to the proposed recommended doses. Interim data are also available for a limited number of subjects with cUTI and cIAI caused by CAZ-NS pathogens from an ongoing open-label Resistant Pathogen study (D4280C00006).

Trial 2001 studied CAZ-AVI with 500 mg ceftazidime + 125 mg avibactam, a dose that was 25% of the dose currently proposed for the treatment of cUTI. The most informative clinical observations demonstrating the added benefit of avibactam were based on a limited number of subjects with infections caused by CAZ-NS pathogens. Among treated subjects who had an adequate baseline culture (mMITT population), 63.0% (29/46) in the CAZ-AVI group achieved both clinical cure and microbiologic eradication at the Test of Cure (TOC) visit compared to 51.0% (25/49) of subjects treated with imipenem-cilastatin. In the subgroup with a CAZ-NS pathogen, 57.1% (8/14) of CAZ-AVI treated subjects achieved both clinical cure and microbiologic eradication compared to 38.9% (7/18) in the imipenem group. All CAZ-NS pathogens in the CAZ-AVI group were *Escherichia coli*.

Trial 2002 studied the 2.5 gram dose of CAZ-AVI (2 g ceftazidime + 0.5 g avibactam) using a 30 minute infusion. In the mMITT population, a favorable clinical response was achieved in 82.4% (70/85) of subjects treated with CAZ-AVI + metronidazole versus 88.8% (79/89) treated with meropenem. In the subgroup of subjects with infections caused by CAZ-NS pathogens, clinical response was 90.0% (27/30) in the CAZ-AVI group and 82.6% (19/23) in the meropenem group. The most common CAZ-NS pathogens in the CAZ-AVI group were *E. coli* and *Klebsiella pneumoniae*. Based on pharmacokinetic analysis of systemic exposure and joint target attainment for pathogens with higher MICs, the proposed regimen for both cUTI and cIAI includes the recommendation for infusions to be given over 2 hours rather than 30 minutes.

Interim data from the ongoing Resistant Pathogen Study (using the final proposed dose of 2.5 grams IV infused over 2 hrs q8h for both cUTI and cIAI caused by CAZ-NS pathogens) included 4 subjects with cIAI and 44 subjects with cUTI. Nineteen of 21 subjects (90.5%) with cUTI were clinical cures compared to 18 of 23 (78.3%) subjects with best-available therapy (BAT). One patient with cIAI was treated with CAZ-AVI and was a clinical cure, whereas 1 of 3 subjects treated with BAT was a clinical cure at TOC.

A Phase 3 HABP/VABP trial is ongoing, however, from the data submitted in this application there are currently no clinical trial data available to be able to assess the benefit of CAZ-AVI for the treatment of HABP/VABP or bacteremia. (b) (4) Two Phase 3 trials, one each in cUTI and cIAI, were recently completed with only top-line results available from the cIAI trial (combined protocols D4280C00001/5, also referred to as RECLAIM).

Additional clinical experience with CAZ-AVI from these Phase 3 trials in the treatment of infections with ceftazidime MICs > 8 mg/L will be needed for more formal inference testing. Despite the limitations to draw conclusions about the contribution of avibactam in preserving activity of ceftazidime by CAZ-NS pathogens from clinical data that are currently available, CAZ-AVI appears to be poised to address an important unmet need for the treatment of cUTI or cIAI caused of multi-drug resistant gram-negative pathogens.

6.1 Indication: Complicated Urinary Tract Infections (cUTI)

NXL104/2001 (Trial 2001)

Primary objectives

• To estimate the by-patient microbiological response of CAZ-AVI in the treatment of adult patients with cUTI in the microbiologically evaluable population compared to imipenem-cilastatin at the TOC visit 5 to 9 days post-therapy.

• To evaluate the safety and tolerability profile of CAZ-AVI in the treatment of cUTI in adults.

Secondary objectives

• To estimate the clinical outcome of CAZ-AVI in the treatment of patients with cUTI at the end of IV therapy, the TOC visit 5 to 9 days post-therapy and at the LFU visit (4 to 6 weeks post-therapy) compared to imipenem-cilastatin in the clinically evaluable population.

• To estimate the by-pathogen microbiological response of CAZ-AVI in the treatment of patients with complicated urinary tract infections (cUTI) in the microbiologically evaluable population compared to imipenem-cilastatin at the end of IV therapy, the TOC visit 5 to 9 days post-therapy and the LFU visit.

• To estimate the by-patient microbiological response of CAZ-AVI in the treatment of patients with cUTI at the end of IV therapy and at the LFU visit compared to imipenem-cilastatin.

Medical Officer comment: This Phase 2 was designed to provide an initial estimate of the efficacy and safety of the selected dosing regimen, but not as a "pivotal" trial with formal hypotheses and pre-specified inferential testing. It was conducted prior to most recent (February 2012) Draft Guidance for cUTI[10], which recommends using the combined clinical and microbiological response at the test-of-cure (TOC) visit in the mMITT population. With the option for an IV to oral switch (when there is no equivalent oral formulation), subjects should have no less than 5 days of IV therapy in order to allow enough time for proper assessment of the IV drug's safety and efficacy for treatment of cUTI. Four days of IV therapy may be acceptable with an interim assessment of symptoms at the end of IV therapy. Important secondary endpoints include continued resolution of symptoms and microbiological success at a TOC approximately 14 days after completion of therapy.

Study dates: 6 November 2008 to 15 June 2010

6.1.1 Methods

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. Complicated UTI 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 could have been enrolled before urine culture results were available if it was likely the results were (based on urinalysis and clinical findings) to be positive. However, if the admission urine culture did not contain a recognized uropathogen in any amount, the subject should have been withdrawn from the study. Subjects whose admission urine culture contained a uropathogen at a count of $< 10^5$ CFU/mL should have remained in the study for the intent-to-treat (ITT) analysis. Subjects who had an indwelling catheter and positive urine culture had their catheter removed or replaced (this criterion was added to the protocol in an amendment dated 19 January 2009). Patients with complete obstruction of any portion of the urinary tract, perinephric/intrarenal abscess, prostatitis, ileal loops, vesico-ureteral reflux, or whose indwelling catheters could not be removed at the time of study entry (e.g. nephrostomy tubes) were excluded. Patients with an estimated creatinine clearance (CrCL) less than 70mL/min by Cockcroft-Gault formula, patients receiving either hemodialysis or peritoneal dialysis, or renal transplant patients were also 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 with a repeat urine culture obtained prior to the switch. The following conditions must have been met: afebrile for at least 24 hours; maximal daily body temperature <37.8°C (<100°F) orally, <38.2°C (<100.8°F) by tympanic measurement, or <38.4°C (<101.0°F) rectally without the influence of antipyretics. Nausea and vomiting must have resolved and improvement must have been noted in most of the following signs and symptoms without evidence of worsening: chills, flank pain, costovertebral angle (CVA) tenderness, dysuria, urgency, frequency, incontinence, and suprapubic pain, as assessed by severity scoring (none, mild, moderate, or severe). If present at baseline, leukocytosis must also have improved (i.e., declined by at least 25%). No oral or parenteral concomitant antimicrobial treatments were permitted while receiving study medication. The use of such antimicrobial treatments other than the study medication for the treatment of the index infection was considered a treatment failure.

Subjects received a minimum of 7 days and a maximum of 14 days of total therapy (IV plus oral). An overall clinical assessment, detailed description and evaluation of the infectious process, urinalysis, safety laboratory assessments, and quantitative urine cultures were performed at baseline, during IV study therapy (Day 3, 4, or 5), at the discontinuation of IV therapy (EOIV), at the TOC visit 5 to 9 days post-therapy, and at 4 to 6 weeks post-therapy (late follow-up or LFU). Subjects on IV therapy at Day 6 to 8, 9 to 11 and 12 to 14 were also assessed for safety laboratory assessments on Day 7, 10 and 13, respectively (±1 day in each case).

The primary efficacy assessment was the microbiological response in the microbiologically evaluable population at the TOC visit, 5 to 9 days post-therapy. Secondary efficacy variables included microbiological outcome per patient at the end of IV therapy and at late follow-up visit and microbiological outcome per pathogen at the end of IV therapy, at Test of Cure visit and at the late follow-up visit.

At the EOIV and the TOC visits, microbiological response was determined as favorable (eradication) or unfavorable (persistence or persistence with acquisition of resistance) for each subject by comparing the urine culture results at follow-up to those at admission. At the LFU visit, microbiological response was defined as favorable (sustained eradication) or unfavorable (recurrence or recurrence with acquisition of resistance). For a favorable microbiological response, pathogens isolated at admission to the study at $>10^5$ CFU/mL must, at follow-up, must have met the CFU criteria for eradication from urine (reduced to $< 10^4$ CFU/mL) and the pathogen must not have been present in blood. If more than one causative pathogen was isolated from the pre-treatment culture(s), and the microbiological response was not the same for all pathogens, the subject was classified as having an unfavorable response if the response of at least one pathogen falls into this category.

Clinical response at EOIV or TOC was recorded by a blinded investigator as "clinical cure" or "clinical failure" based on whether all or most pre-therapy signs and symptoms of the index infection had resolved and no additional study drug was required. A subject was considered to have had an "indeterminate" response if there was a loss to follow-up such that a determination of clinical response cannot be made. Response assessed at LFU was either a "sustained clinical cure", "clinical failure", "clinical relapse" or "indeterminate".

Medical Officer comment: For the purpose of analyses in this review, a "clinical cure" at TOC will be considered a favorable outcome. Either a "clinical failure" or "indeterminate" will be an unfavorable outcome.

Descriptive summaries (i.e. response rates, 95% 2-sided CIs and differences between treatment groups with 95% 2-sided CIs) were provided for each of the primary and secondary variables.

6.1.2 Demographics

Overall, 135 subjects were randomized, including 68 in the CAZ-AVI group and 67 in the IMI-CS group. Comparability of treatment groups by baseline demographics are summarized in Table 28.

Table 28: 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)	49.9 (18.4)	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)	55 (82.1)	112 (83.0)
	65 ≤ Age < 75	5 (7.4)	2 (3.0)	7 (5.1)
	Age 75 and over	6 (8.8)	10 (14.9)	16 (11.9)
Gender	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

Medical Officer comment: Few subjects treated with CAZ-AVI were older than the age of 65 (six subjects) or black/African American (two subjects). Most (approximately 75%) were female, which is consistent with other cUTI trials. Subjects were generally similar across the treatment groups in age, gender, race and ethnicity.

Enrollment by country is summarized in Table 29. Approximately 15% were recruited in the US.

Table 29: Summary by Country for Trial 2001—Safety Population

Country	CAZ-AVI (N=68) n (%)	IMI-CS (N=67) n (%)	Overall (N=135) n (%)
Guatemala	16 (23.5)	17 (25.4)	33 (24.4)
India	7 (10.3)	5 (7.5)	12 (8.9)
Jordan	12 (17.6)	11 (16.4)	23 (17.0)
Lebanon	22 (32.4)	25 (37.3)	47 (34.8)
USA	11 (16.2)	9 (13.4)	20 (14.8)

6.1.3 Subject Disposition

Subject disposition in Trial 2001 is summarized in the following table (Table 30). Approximately 77% of subjects completed their treatment and 75% completed the study. Of the subjects who discontinued treatment, the majority (13 patients in the CAZ-AVI group and 10 patients in the IMI-CS group) did so because they "did not meet inclusion/exclusion criteria". These subjects were enrolled based on Gram stain results that showed gram-negative bacteria, but had no subsequent growth on the baseline culture.

Table 30: Subject Disposition in Trial 2001

	CAZ-AVI (N=69) n (%)	IMI-CS (N=68) n (%)	Total (N=137) n (%)
Randomized	**69**	**68**	**137**
Did not receive study medication	**1**	**1**	**2**
Completed the study treatment	**50 (72.5%)**	**56 (82.4%)**	**106 (77.4%)**
Did not complete the study treatment	**18 (26.1%)**	**11 (16.2%)**	**29 (21.2%)**
Did not meet inclusion/exclusion criteria	13 (18.8%)	10 (14.7%)	23 (16.8%)
Discontinued due to serious adverse event	1 (1.4%)	0	1 (0.7%)
Investigator decision	0	1 (1.5%)	1 (0.7%)
Protocol deviation	1 (1.4%)	1 (1.5%)	2 (1.5%)
Withdrew consent	2 (2.9%)	0	2 (1.5%)
Lost to follow-up	1 (1.4%)	0	1 (0.7%)
Other	1 (1.4%)	0	1 (0.7%)
Completed the study	**49 (71.0%)**	**54 (79.4%)**	**103 (75.2%)**
Did not complete the study	**20 (29.0%)**	**14 (20.6%)**	**34 (24.8%)**
Did not meet inclusion/exclusion criteria	13 (18.8%)	11 (16.2%)	24 (17.5%)
Discontinued due to serious adverse event	1 (1.4%)	0	1 (0.7%)
Withdrew consent	2 (2.9%)	0	2 (1.5%)
Protocol deviation	1 (1.4%)	0	1 (0.7%)
Lost to follow-up	2 (2.9%)	3 (4.4%)	5 (3.6%)
Other	1 (1.4%)	0	1 (0.7%)

The analysis populations are as follows and enumerated in Table 31.

ITT: All randomized subjects

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.

CE (Clinically Evaluable) population was defined as all subjects who:

- Had clinical evidence of UTI
- Were compliant with study drug therapy (received at least 7 total days of antibacterial therapy) or classed as an evaluable clinical failure after completing at least 48 hours of IV study therapy.
- Had a clinical outcome assessment at TOC visit

Table 31: Trial 2001 Analysis Groups— Randomized (ITT) Population

	CAZ-AVI (N=69) n (%)	IMI-CS (N=68) n (%)	Total (N=137) n (%)
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)
CE	28 (40.6)	36 (52.9)	64 (46.7)

Medical Officer comment: This review will prioritize analyses based on the mMITT population, which helps to preserve the effect of randomization. Lack of a qualifying urine culture, however, may be affected by use of prior antimicrobials. The ME population and the CE populations are subgroups that exclude subjects based on post-randomization criteria and could potentially introduce bias. Additionally, analyses in the ME and CE populations are limited given the large number (almost 55%) of subjects excluded. In accordance with current regulatory guidance and FDA recommendation at the Pre-NDA meeting on 19 Dec 2013, the Sponsor considered microbiological outcome at TOC in the mMITT population as the primary endpoint in their Integrated Summary of Efficacy.

Approximately two-thirds of patients enrolled in either treatment group had acute pyelonephritis, including 44 patients (64.7%) in the CAZ-AVI group and 41 patients (61.2%) in the IMI-CS group. Primary diagnoses and urinary tract abnormalities for subjects included in the mMITT population are provided in Table 32.

Table 32: Summary of Primary Diagnoses—mMITT Population

	CAZ-AVI (N=46) n (%)	IMI-CS (N=49) n (%)	Total (N=95) n (%)
Acute Pyelonephritis	30 (65.2)	29 (59.2)	59 (62.1)
Other cUTI without acute pyelonephritis	16 (34.8)	20 (40.8)	36 (37.9)
Urinary tract abnormalities at baseline	15 (32.6)	20 (40.8)	35 (36.8)
Partial obstructive uropathy, acquired	5 (10.9)	4 (8.2)	9 (9.5)
Structural abnormality	1 (2.2)	3 (6.1)	4 (4.2)
Elevated post voiding residual volume (≥100 mL)	0	4 (8.2)	4 (4.2)
Neurogenic bladder	5 (10.9)	2 (4.1)	7 (7.4)
Other	5 (10.9)	10 (20.4)	15 (15.8)
Baseline bacteremia	3 (6.5)	4 (8.2)	7 (7.4)
Concurrent bacteremia with pathogen isolated from urine	3 (6.5)	3 (6.1)	6 (6.3)

Note: Subjects may be counted in more than 1 category. Data source: adapted from Sponsor's Tables 2.2.1.3.1–1 and 2.2.1.3.2–1, ISE for cUTI

Prior and Concomitant Antibacterial Therapy

As stated in the protocol, patients were excluded if they had received ≥ 1 dose of another potentially effective systemic antibiotic after obtaining the initial urine culture or if they had received > 1 dose of a potentially effective systemic antibiotic therapy within 48 hours before the admission culture specimen had been obtained. Patients who received prior antibiotics and did not respond may still have been eligible for enrollment if (all of the following):

- Failure/lack of response is due to a pathogen that had documented resistance to the original antibiotic therapy
- The urine culture was still positive (containing ≥ 10^5 CFU/mL)
- The pathogen was susceptible to CAZ-AVI and imipenem
- Permission was granted by the medical monitor

No oral or parenteral concomitant antimicrobial treatments were permitted while receiving study medication. A patient requiring additional antimicrobial treatment other than the study medication for the treatment of his or her complicated urinary tract infection was considered a treatment failure.

As shown in Table 33, 13 patients (7 in CAZ-AVI and 6 in IMI-CS) in Trial 2001 received prior antibacterial therapy. The most common antibiotic used was ceftriaxone (4 subjects) in the CAZ-AVI group and ciprofloxacin (5 subjects) in the IMI-CS group. There is an imbalance in the receipt of concomitant antibiotic used; however, most subjects who received an additional antibiotic did so after TOC. Five subjects received a concomitant antibiotic in the CAZ-AVI group and 21 in the IMI-CS group. The most commonly used medications concomitantly with the study drug were amoxicillin-clavulanate, ciprofloxacin, imipenem (3 patients in the IMI-CS group), and metronidazole. Ciprofloxacin allowed in the protocol as an oral switch.

Table 33: Use of Prior and Concomitant Antibacterial Medications—mMITT Population

	CAZ-AVI (N=46) n (%)	IMI-CS (N=49) n (%)	Total (N = 95) n (%)
Prior Antibacterial Medication	7 (15.2)	6 (12.2)	13 (13.7)
Concomitant Antibacterial Medication	5 (10.9)	21 (42.9)	26 (27.4)

6.1.4 Analysis of Primary Endpoints

The protocol-specified primary endpoint was microbiologic response in the ME population at the TOC Visit (5 to 9 days post-therapy). Table 34 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 34: 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	

Table 35 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%). Although not pre-specified, the combined outcome (clinical + microbiological) in the mMITT population at TOC is highlighted here as the endpoint of primary interest.

Table 35: 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)	
Combined Clinical + Microbiological Response			
Cure + Eradication	29 (63.0)	25 (51.0)	12.0 (-9.1, 31.7)
Failure + Persistence or Indeterminate	17 (37.0)	24 (49.0)	

*Exact 95% Clopper-Pearson confidence intervals

Medical Officer comment: Clinical and microbiologic response rates in the Phase 2 cUTI study appeared to be lower than expected for both arms. In an Information Request, DAIP asked the Applicant to provide their assessment. In response, they used a meta-analysis of comparative trials to provide an estimate of the treatment effect of ceftazidime alone in cUTI as well as other contemporary Phase 3 cUTI trials. Direct comparisons with these trials were limited due to the following explanations: some studies allowed co-administration of effective systemic antimicrobial therapy, ceftazidime dosing in the historical studies was variable (ranging from 1 to 6 g total daily dose and duration of therapy ranged from 3 to 21 days), and use of different comparators. In subset analyses by dose, they also offered a rationale that supported using an increased dose of ceftazidime in the treatment of cUTI, particularly for organisms with higher MICs such as *P. aeruginosa*.

Based on the FDA's summary of similar Phase 3 trials that evaluated responses at end of IV therapy (a meta-analysis of microbiological success + clinical response, as presented in the 2012 FDA Draft Guidance for cUTI[10]), a historical treatment effect was estimated at 64% (95% CI: 56%, 72%). An estimated putative placebo response or natural history outcome, based on four studies before the availability of antibacterial drug therapies, was 25.6% (95% CI: 19.6%, 32.7%). By comparison, the point estimate of 63.0% in Trial 2001 is bounded by a 95% CI of 48.0% and 78.0%. Although the lower limit of the 95% CI in the CAZ-AVI group is 15.3% greater than the upper limit of untreated group, there remain several uncertainties in making this comparison. Any non-inferiority assessment should also be interpreted with caution given the

lack of pre-specified hypothesis testing criteria, questionable consistency with other contemporary trials and a lower than expected clinical and microbiological response.

6.1.5 Analysis of Secondary Endpoints

Additional protocol-specified endpoints included the following:

- Clinical response in the CE population at the EOIV, TOC and LFU
- Microbiological response in the ME population at EOIV and LFU
- Microbiological response in the ME population by-pathogen at EOIV, TOC and LFU

Medical Officer comment: Observed differences (with 95% CIs) are not presented in this review. Analyses are presented only for descriptive purposes and hypothesis generation. Imbalance of numbers of subjects included in CE and ME analysis populations between treatment arms indicates likelihood of the introduction of a number of potential post-randomization biases; therefore, analyses will be presented in the mMITT population.

Summaries of each of these analyses are presented in Table 36, Table 37 and Table 38, respectively.

Table 36: Clinical Outcome by Visit—mMITT Population

Visit Outcome	CAZ-AVI (N=46) n (%)*	IMI-CS (N=49) n (%)*
EOIV		
Clinical Cure	43 (93.5)	46 (93.9)
Clinical Failure	0	2 (4.1)
Indeterminate	3 (6.5)	1 (2.0)
TOC		
Clinical Cure	37 (80.4)	36 (73.5)
Clinical Failure	5 (10.9)	9 (18.4)
Indeterminate	4 (8.7)	4 (8.2)
LFU		
Sustained Clinical Cure	33 (71.7)	32 (65.3)
Clinical Failure (carried forward from TOC)	5 (10.9)	9 (18.4)
Clinical Relapse	3 (6.5)	6 (12.2)
Indeterminate	5 (10.9)	2 (4.1)

Source: Adapted from Tables 2.2.1.6.2.3–1 and 2.2.1.6.2.4–1, Sponsor's ISE for cUTI; *Percentages are based on total at each visit

Table 37: Microbiological Outcome by Visit—mMITT Population

Visit Outcome	CAZ-AVI (N=46) n (%)*	IMI-CS (N=49) n (%)*
EOIV		
Eradication	40 (87.0)	45 (91.8)
Persistence	1 (2.2)	0
Indeterminate	5 (10.9)	4 (8.2)
TOC		
Eradication	31 (67.4)	31 (63.3)
Persistence	10 (21.7)	14 (28.6)
Indeterminate	5 (10.9)	4 (8.2)
LFU		
Sustained eradication	23 (50.0)	23 (46.9)
Recurrence	7 (15.2)	3 (6.1)
Persistence	10 (21.7)	14 (28.6)
Indeterminate	6 (13.0)	9 (18.4)

Source: Table 14.2.1.3 Study NXL104/2001 CSR; *Percentages are based on total excluding indeterminate

Table 38: Favorable Microbiological Outcome by Pathogen and Visit—mMITT Population

Visit Pathogen	CAZ-AVI (N=46) n (%)[a]	IMI-CS (N=49) n (%)[a]
EOIV		
Escherichia coli [b]	39/43 (90.7)	39/42 (92.9)
Pseudomonas aeruginosa	1/3 (33.3)	2/2 (100.0)
Citrobacter koseri [b]	1/1 (100.0)	0/0
Enterobacter aerogenes	0/0	1/1 (100.0)
Enterobacter cloacae	0/0	1/1 (100.0)
Klebsiella oxytoca	0/0	0/1
Morganella morganii	0/0	1/1 (100.0)
Proteus mirabilis	0/0	1/1 (100.0)
TOC		
Escherichia coli [b]	31/43 (72.1)	26/42 (61.9)
Pseudomonas aeruginosa	0/3	0/2
Citrobacter koseri [b]	1/1 (100.0)	0/0
Enterobacter aerogenes	0/0	1/1 (100.0)
Enterobacter cloacae	0/0	1/1 (100.0)
Klebsiella oxytoca	0/0	1/1 (100.0)
Morganella morganii	0/0	1/1 (100.0)
Proteus mirabilis	0/0	1/1 (100.0)
LFU		
Escherichia coli [b]	23/43 (53.5)	19/42 (45.2)
Pseudomonas aeruginosa	0/3	0/2
Citrobacter koseri [b]	1/1 (100.0)	0/0
Enterobacter aerogenes	0/0	1/1 (100.0)
Enterobacter cloacae	0/0	0/1
Klebsiella oxytoca	0/0	1/1 (100.0)
Morganella morganii	0/0	1/1 (100.0)
Proteus mirabilis	0/0	1/1 (100.0)

Source: Adapted from Sponsor's Tables 14.2.3.1.2, 14.2.3.2.2 and 14.2.3.3.2 in the ISE for cUTI. [a] Percentages are based on favorable assessment/number of pathogens; [b] One patient (20413) in the CAZ-AVI group had both *E.coli* and *C.koseri* isolated.

Medical Officer comment: For further evaluation of the primary endpoint recommended in the Draft Guidance for cUTI (resolution of symptoms and microbiological success at TOC), outcomes were also evaluated by baseline pathogen, as shown in Table 39.

E. coli was the most common uropathogen, and was eradicated in 26/40 (65.0%) subjects with the combined clinical + microbiologic cure in the CAZ-AVI group and 22/41 (53.7%) subjects in the IMI-CS group. The number of subjects with a pathogen other than *E. coli* was extremely small, prohibiting comparisons across treatment groups. There were two subjects with two or more baseline pathogens: Subject 20413 had *C. koseri* and *E. coli* in the CAZ-AVI group and Subject 40008 in the IMI-CS group had *A. baumanii*, *A. junii*, and *P. aeruginosa.*

Table 39: 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)

Medical Officer comment: Note that in this analysis, *A. baumannii* and *A. junii* were listed as pathogens in the IMI-CS arm, whereas the Sponsor's analyses did not account for these pathogens. Subject 40008 only had *P. aeruginosa* identified from a urine specimen, with the other two identified only in blood. Therefore, in the preceding tables based on the Sponsor's analysis, *A. baumanii* or *A. junii* were not considered uropathogens.

Subjects in the mMITT Population who were microbiological failures at TOC are summarized in Table 40.

Medical Officer comment: The characteristics of these subjects did not appear different from the characteristics of subjects overall in the study; however, the number of microbiological failures was small (10 in the CAZ-AVI group and 14 in the IMI-CS group). Nevertheless, the overall (clinical or microbiological) failure rate in cUTI trial was high (37%), for which it was unclear how much could be contributed to PK/PD considerations (i.e. inadequate dose). Since only a few these subjects had pathogens such as *P. aeruginosa* with high MIC's, however, another consideration is a number of subjects in the mMITT population who did not meet the appropriate criteria for cUTI diagnosis.

Table 40: Subjects with Microbiological Persistence at TOC—mMITT Population

Subject	Population(s) (Reason Excluded from ME Population)	Age	Primary Diagnosis	Uropathogen [a]	TOC MIC [b] (mg/L)
CAZ-AVI					
20213	ME and mMITT	64	Pyelonephritis	*E. coli*	0.12
20313	ME and mMITT	50	Pyelonephritis	*E. coli*	0.12
20407	ME and mMITT	67	Pyelonephritis	*E. coli*	0.12
30106	ME and mMITT	36	cUTI	*P. aeruginosa*	2
30108	ME and mMITT	57	Pyelonephritis	*E. coli*	0.12
30202	ME and mMITT	28	Pyelonephritis	*E. coli*	0.12
30203	ME and mMITT	39	cUTI	*E. coli*	0.25
30210	mMITT only (did not meet cUTI/pyelonephritis definition)	28	cUTI	*E. coli*	0.06
40001	mMITT only (violation of assessment time schedule)	49	cUTI	*E. coli*	0.12
50105	ME and mMITT	27	cUTI	*P. aeruginosa*	4
IMI-CS					
11001	mMITT only (received concomitant antibiotic)	63	Pyelonephritis	*P. aeruginosa*	0.5
20202	ME and mMITT	20	Pyelonephritis	*E. coli*	0.12
20305	ME and mMITT	27	cUTI	*E. coli*	0.12
20402	ME and mMITT	34	Pyelonephritis	*E. coli*	0.12
20411	ME and mMITT	77	Pyelonephritis	*E. coli*	0.12
30002	ME and mMITT	45	cUTI	*E. coli*	0.12
30201	ME and mMITT	52	cUTI	*E. coli*	0.25
30209	ME and mMITT	50	cUTI	*E. coli*	0.06
30211	mMITT only (did not meet cUTI/pyelonephritis definition)	21	Pyelonephritis	*E. coli* *E. coli*	0.12 0.06
30213	mMITT only (did not meet cUTI/pyelonephritis definition)	56	Pyelonephritis	*E. coli*	0.12
40008	mMITT only (resistant pathogen)	36	cUTI	*P. aeruginosa*	16
40111	ME and mMITT	29	cUTI	*E. coli*	0.06
40209	ME and mMITT	54	Pyelonephritis	*E. coli*	0.06
40304	ME and mMITT	47	Pyelonephritis	*E. coli*	0.12

Source: Table 2.2.1.6.1–2 in the Sponsor's ISE for cUTI. [a] From urine culture. [b] MIC of CAZ-AVI for the CAZ-AVI groups and imipenem for the imipenem group

6.1.6 Other Endpoints

For exploratory purposes, emergent infections (i.e. superinfections or new infections) and mortality were considered as additional endpoints in this review. A superinfection was defined as growth of a pathogen other than a baseline pathogen during the course of study drug therapy from any site of infection. No subjects developed superinfections during study therapy. A new infection was defined as growth of a pathogen other than a baseline pathogen after the completion of study drug therapy from any site of infection. In the mMITT population, there was one subject with one new infection caused by *Pseudomonas aeruginosa* in the CAZ-AVI group. In the IMI-CS group, there were 10 subjects with 16 new infections. All pathogens

involved in new infections were isolated from urine; there were no new infections at other sites. *Klebsiella pneumoniae* was the most common uropathogen involved in new infections, all cases occurring in the IMI-CS group.

There were no deaths in the CAZ-AVI group. One subject (Subject 20304) in the IMI-CS group died; however, the cause of death appeared to be unrelated to the index cUTI. The clinical response at TOC was indeterminate because the subject was not evaluated at TOC or LFU and was considered lost to follow up. According to the narrative provided, this subject was an 83-year-old female, whose baseline urine culture grew *E. coli*. She received IMI-CS for 11 days and was discharged home on Study Day 13. On Day 21, the subject was readmitted with urosepsis, which was reported as an SAE. On Day (b) (6), a sigmoidoscopy showed multiple diverticula and a vesicorectal fistula. She underwent sigmoidectomy and closure of the bladder with creation of colostomy and right-sided ureterostomy. Following a subsequent rupture of the urinary bladder, she received only palliative care and died on Day (b) (6).

6.1.7 Subpopulations

In the analyses based on demographic subpopulations, the numbers within each subgroup were small, so only the microbiological outcome is presented. Table 41 summarizes microbiological outcome at TOC by gender, age and race in the mMITT population. No Native Hawaiian, Pacific Islander, American Indian or Alaskan Native subjects were included.

Medical Officer comment: Although numbers were small, differences of underlying anatomy between male and female subjects and baseline urinary tract abnormalities likely contributed to differences in outcome. Interpretation of any imbalance between outcomes in other subgroups is limited.

Table 41: Summary of Microbiological Outcome at TOC by Demographic Group—mMITT Population

Demographic Subgroup	CAZ-AVI (N= 46) n/N (%)	IMI-CS (N= 49) n/N (%)
Overall	31/46 (67.4)	31/49 (63.3)
Gender		
Male	7/9 (77.8)	11/14 (78.6)
Female	24/37 (64.9)	20/35 (57.1)
Age Category		
18 to 64	28/41 (68.3)	24/40 (60.0)
≥65	3/5 (60.0)	7/9 (77.8)
≥75	1/2 (50.0)	5/7 (71.4)
Race		
White or Caucasian	17/29 (58.6)	17/32 (53.1)
Black/African American	1/1 (100.0)	4/4 (100.0)
Asian	3/4 (75.0)	3/3 (100.0)
Other	10/12 (83.3)	7/10 (70.0)
Ethnicity		
Hispanic or Latino	10/12 (83.3)	8/12 (66.7)
Not Hispanic or Latino	21/34 (61.8)	23/37 (62.2)
Region		
US	5/8 (62.5)	4/6 (66.7)
Rest of World	26/38 (68.4)	27/43 (62.8)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Refer to 6.2.8 for additional discussion of outcomes by CAZ-AVI MIC and the rationale for susceptibility interpretive criteria.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

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 42), but half of these subjects later experienced clinical relapse at LFU.

Table 42: 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.

6.1.10 Additional Efficacy Issues/Analyses

Table 43 presents the primary endpoint, clinical response and microbiological outcome, as observed in 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 43: 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)	

*Exact 95% Clopper-Pearson confidence intervals

Medical Officer comment: Although outcomes in the CAZ-AVI arm within the CAZ-NS subgroup allow for an assessment of the contribution of avibactam in restoring activity of ceftazidime, it is not necessarily a valid comparison when using a carbapenem as a comparator, since resistance to ceftazidime may not imply resistance to imipenem (resistance to imipenem is expected to be less likely). Dr. Gamalo, the statistical reviewer, conducted an additional analysis in order to assess the rate of imipenem resistance in the IMI-CS group and also make an estimate of inadequate therapy (or "putative placebo") based on response rates among subjects who had imipenem-resistant isolates. Because only two subjects received inadequate therapy, however, the confidence interval is wide. With this degree of uncertainty, no meaningful inference can be made.

Table 44 shows the results for the combined clinical + microbiologic response by treatment and susceptibility to ceftazidime in the CAZ-AVI arm and imipenem in the IMI-CS arm. Subjects in the IMI-CS arm whose baseline isolates were non-susceptible to imipenem were considered a "putative placebo" group since these subjects received inadequate therapy based on in vitro culture results. 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 cure rate in the CAZ-AVI group in the mMITT population is 63.0% (highlighted in Table 35), whereas 1 of 2 (50.0%) subjects with inadequate therapy responded (highlighted in Table 44). 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%).

Table 44: Clinical Response and Microbiologic Outcome by Treatment and Susceptibility to Ceftazidime or Imipenem—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.

Favorable microbiological response by uropathogen at TOC is shown in Table 45. As was noted in Table 39, *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 45: 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	16
Escherichia coli	8/14 (57.1)	7/18 (43.8)
Enterobacter cloacae	0	0/1 (0.0)
Pseudomonas aeruginosa	0	0/1 (0.0)

Clinical cure at TOC (not necessarily accounting for microbiologic eradication) in subjects with a CAZ-NS uropathogen is shown in Table 46 by baseline diagnosis (with pyelonephritis or without acute pyelonephritis) or by baseline pathogen. Concurrent bacteremia at baseline with the uropathogen isolated from urine was infrequent, occurring in only 6 subjects in the mMITT population. Of the seven subjects with bacteremia at baseline, 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.

Table 46: 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.

In the following table, Table 47, microbiologic outcomes at TOC are summarized in subgroups of subjects by baseline MIC to ceftazidime.

Table 47: Favorable Microbiologic Outcome at TOC by Treatment Group and Baseline Uropathogen Minimum Inhibitory Concentration (MIC) to Ceftazidime—mMITT Population

Pathogen MIC (mg/L)	CAZ-AVI (N=46) n/N (%)	IMI-CS (N=49) n/N (%)
Enterobacteriaceae		
Isolated	43	47
Tested	41	46
≤0.03	0/0	2/2 (100.0)
0.06	3/4 (75.0)	1/1 (100.0)
0.12	13/15 (86.7)	11/15 (73.3)
0.25	2/3 (66.7)	3/5 (60.0)
0.5	0/1 (0.0)	2/3 (66.7)
1	1/2 (50.0)	2/2 (100.0)
2	2/2 (100.0)	0/1 (0.0)
8	0/2 (0.0)	0/1 (0.0)
16	3/3 (100.0)	2/3 (66.7)
32	6/9 (66.7)	8/13 (61.5)
Pseudomonas aeruginosa		
2	0/1 (0.0)	0/0
4	0/2 (0.0)	0/1 (0.0)
32	0/0	0/1 (0.0)

Source: Table 2.5.1.5, 2.7.2 Summary of Clinical Pharmacology. Baseline uropathogens and blood isolates that are also baseline uropathogens are included. For subjects with the uropathogen found in the blood also, the highest MIC is shown in mg/L. N = Number of subjects in the mITT Population. N1 = Number of Subjects with the specified organism at the given MIC level. n = Number of subjects with favorable response for the organism at the given MIC level. Percentages are calculated as 100 × (n/N1).

Table 48: Summary of Microbiological Outcome by β-lactamase Status—mMITT Population, Ceftazidime-Resistant Urinary Isolates

Pathogen	β-lactamase	CAZ-AVI (N=44) n/m (%)	IMI-CS (N=48) n/m (%)
Escherichia coli		9/12 (75.0)	9/15 (60.0)
	CTX-M-15	8/10 (80.0)	9/14 (64.3)
	TEM-1	6/8 (75.0)	3/9 (33.3)
	OXA-30	6/7 (85.7)	2/4 (50.0)
	CMY-2	0/2 (0.0)	0/1 (0.0)
	SHV-12	1/1 (100.0)	
	upregulated *ampC*	1/1 (100.0)	1/1 (100.0)
Enterobacter cloacae			1/1 (100.0)
	TEM-1		1/1 (100.0)
	upregulated *ampC*		1/1 (100.0)
Pseudomonas aeruginosa			0/1 (0.0)
	TEM-1		0/1 (0.0)
	upregulated *ampC*		0/1 (0.0)

Source: Table 4, Sponsor's Addendum to the CSR for Trial 2001. Ceftazidime resistance was defined as MIC ≥ 16 µg/mL for Enterobacteriaceae, and ≥ 32 ug/mL for *P. aeruginosa* and other non-fermentative gram-negative bacteria. N: number of patients in MITT population for each treatment group. n = number of subjects with microbiologic eradication of the specific pathogen. m = number of subjects with pathogen/β-lactamase status at the baseline visit.

6.2 Indication: Complicated Intra-Abdominal Infections

NXL104/2002 (Trial 2002)

Primary objective

- To estimate the efficacy of CAZ-AVI plus metronidazole (MTZ) with respect to the clinical response in baseline microbiologically evaluable patients with cIAI at the TOC visit, 2 weeks post-treatment, compared to meropenem.

Secondary Objectives

- To evaluate the safety and tolerability profile of CAZ-AVI + MTZ in the treatment of cIAI in adults.
- To estimate the efficacy of CAZ-AVI +MTZ with respect to the clinical response in baseline microbiologically evaluable patients with cIAI at EOIV and at the LFU visit at 4 to 6 weeks post-treatment compared to meropenem.
- To estimate the clinical response of CAZ-AVI + MTZ at EOIV, TOC, and at the LFU visit, 4 to 6 weeks post-treatment compared to meropenem.
- To estimate the microbiological response of CAZ-AVI + MTZ with cIAI at EOIV, TOC, and at LFU at 4 to 6weeks -treatment compared to meropenem.

Medical Officer comment: Trial 2002 was designed to provide an initial estimate of the efficacy and safety of the selected dosing regimen. It was not statistically powered to demonstrate non-inferiority to comparator. There were no formal hypotheses/pre-specified inferential testing.

6.2.1 Methods

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.

For pre-operative enrollment, the following conditions must have been met:

a. Evidence of systemic inflammatory response, with at least one of the following:
    1. Fever (temperature > 37.8°C; > 38°C tympanic; > 38.3°C rectal; or hypothermia with a core body temperature < 35°C
    2. Elevated WBC (> 10,500/mm^3)
    3. Drop in blood pressure (however, systolic BP must be > 90 mm Hg without pressor support)
    4. Increased pulse (HR > 90) and respiratory rates (> 20)
    5. Hypoxemia
    6. Altered mental status

AND

b. Physical findings consistent with intra-abdominal infection, such as:
    1. Abdominal pain and/or tenderness, with or without rebound
    2. Localized or diffuse abdominal wall rigidity
    3. Mass
    4. Ileus

AND

c. Supportive radiologic imaging findings of intra-abdominal infection such as perforated intraperitoneal abscess detected on CT scan, MRI, or ultrasound

AND

d. requirement for surgical intervention, including open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery;

AND

e. Specimens from the surgical intervention are sent for culture and susceptibility testing

AND

f. Infection is caused or presumed to be caused by mircroorganisms susceptible to the intravenous study medications (CAZ-AVI +MTZ or meropenem)

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 AST and/or ALT up to 5 × 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 primary efficacy assessment is the clinical response in the microbiologically evaluable population at the TOC visit, 2 weeks post-therapy. The protocol and SAP stated that the determination of evaluable subject populations and outcomes would be based on Investigator assessments. However, during the blinded data review, it was determined that there were a limited number of instances where the criteria for favorable response were not strictly applied by the Investigator, and subjects were classified as indeterminate rather than failures. A Sponsor-verified set of outcomes was defined in which the outcome for some subjects was deemed to be failure rather than indeterminate failures.

Medical Officer comment: In this review, the primary analysis variable for efficacy is the Sponsor-verified clinical outcome TOC, 2 weeks post-therapy, in the mMITT population.

Clinical and Microbiological Outcome Categories/Responses

An overall clinical assessment (including signs/symptoms of infection and cultures from intra-abdominal site of infection and blood), vital signs, and detailed abdominal assessment were performed at baseline, daily during study therapy, at the discontinuation of study therapy, at the early follow-up or TOC visit (2 weeks post-antibiotic therapy), and at the LFU visit (4 to 6 weeks post-antibiotic therapy). Microbiological assessments including Gram stain, WBC count, and culture were performed on specimens obtained from the intra-abdominal cavity or from the blood at baseline and as appropriate during the course of the study.

Microbiological response was determined for each baseline pathogen isolated from intra-abdominal sites and/or blood at EOIV, TOC, and LFU visits. If no post-baseline microbiological specimen was available for culture, the microbiological response was presumed based on the

clinical response; eradication was presumed for favorable clinical responses and persistence was presumed for all unfavorable clinical responses. Clinical and microbiological outcome definitions are detailed in Table 49.

Table 49: Clinical and Microbiological Outcome Definitions for Trial 2002

Clinical Response	***Definition***
Clinical Cure	Complete resolution or significant improvement of signs and symptoms of the index infection. No further antimicrobial therapy or surgical or radiological intervention is necessary.
Clinical Failure	Death related to intra-abdominal infection at any time point Persisting or recurrent infection within the abdomen documented by the findings at re-intervention either percutaneously or operatively Postsurgical wound infections defined as an open wound with signs of local infection such as purulent exudates, erythema, or warmth that requires additional antibiotics and/or non-routine wound care, or Subjects who receive treatment with additional antibiotics for ongoing symptoms of intra-abdominal infection during the study antibiotic period
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death occurred during the study period and the index infection was clearly noncontributory • Extenuating circumstances preclude classification as cure or failure
Microbiological Response	
Eradication	Absence of causative pathogens from appropriately obtained specimens at the site of infection
Presumptive Eradication	Absence of material to culture in a patient who had responded clinically to treatment.
Persistence	Any causative organism still present at or beyond the end of therapy from a culture of intra-abdominal abscess, peritonitis or surgical wound infection.
Persistence Acquiring Resistance [a]	Continued presence of the original pathogen in cultures from the original site of infection obtained during or upon completion of therapy, and the pathogens that were susceptible to study drug pretreatment have become resistant to study drug therapy (defined as ≥ 4-fold increase in study drug MIC) post-treatment.
Presumed Persistence	Repeat cultures were not obtained because of the absence of material to culture in a patient who was assessed as clinical failure.
Indeterminate	• Entry culture either not obtained or no growth • Assessment not possible because of protocol violation • Any other circumstance which makes it impossible to define the microbiological response.

[a] Only persistence was assessed for CAZ-AVI as breakpoints for CAZ-AVI have not been defined.

6.2.2 Demographics

The demographics of subjects included in the safety population are summarized in Table 50.

Medical Officer comment: Subjects were generally similar across the treatment groups in age, gender, race and ethnicity. No black/African American subjects were included in the CAZ- AVI + MTZ arm. Most were male with median age of 41, which is consistent with other cIAI trials. Few subjects treated with CAZ-AVI were older than the age of 65 (9 subjects, or about 9%). Although mean/median ages similar across both treatment groups, there were more patients ≥65 years of age in the meropenem group (15 subjects) than CAZ-AVI + MTZ (9 subjects).

Table 50: 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)
Gender	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 and metronidazole

Enrollment by country is summarized in Table 51. Approximately 9% were recruited in the US. The majority of subjects were enrolled in India (39.4%) and Russia/Eastern Europe.

Table 51: Summary by Country for Trial 2002—Safety Population

Country	CAZ-AVI + MTZ N=101 n (%)	Meropenem N=102 n (%)	Overall N=203 n (%)
Bulgaria	6 (5.9)	10 (9.8)	16 (7.9)
France	3 (3.0)	0 (0.0)	3 (1.5)
India	44 (43.6)	36 (35.3)	80 (39.4)
Lebanon	3 (3.0)	1 (1.0)	4 (2.0)
Poland	1 (1.0)	0 (0.0)	1 (0.5)
Romania	23 (22.8)	34 (33.3)	57 (28.1)
Russia	9 (8.9)	14 (13.7)	23 (11.3)
USA	12 (11.9)	7 (6.9)	19 (9.4)

6.2.3 Subject Disposition

Subject disposition in Trial 2002 is summarized in the following table (Table 52). Approximately 92% of subjects completed their treatment and follow through to the end of study. Of the subjects who discontinued treatment (11 in the CAZ-AVI + MTZ group and 6 in the meropenem group), the majority did so due to an adverse event, either serious or non-serious. The treatment groups were generally similar with respect to the number and reasons that subjects discontinued from the study.

Table 52: Subject Disposition in Trial 2002

	CAZ-AVI + MTZ (N=102) n (%)	Meropenem (N=102) n (%)	Total (N=204) n (%)
Randomized	**102**	**102**	**204**
Did not receive study medication	**1 (1.0)**	**0**	**1 (0.5)**
Completed the study treatment	**93 (91.2)**	**95 (93.1)**	**188 (92.2)**
Did not complete the study treatment			
Discontinued due to adverse event	4 (3.9)	1 (1.0)	5 (2.5)
Discontinued due to serious adverse event	2 (2.0)	3 (2.9)	5 (2.5)
Investigator decision	1 (1.0)	0	1 (0.5)
Protocol deviation	1 (1.0)	0	1 (0.5)
Lost to follow-up	0	2 (2.0)	2 (1.0)
Other	1 (1.0)	1 (1.0)	2 (1.0)
Completed the study	**91 (89.2)**	**96 (94.1)**	**187 (91.7)**
Did not complete the study	**11 (10.8)**	**6 (5.9)**	**17 (8.3)**
Clinical failure	0	1 (1.0)	1 (0.5)
Discontinued due to adverse event	2 (2.0)	0	2 (1.0)
Discontinued due to serious adverse event	3 (2.9)	3 (2.9)	6 (2.9)
Protocol deviation	1 (1.0)	0	1 (0.5)
Lost to follow-up	1 (1.0)	2 (2.0)	3 (1.5)
Other	4 (3.9)	0	4 (2.0)

The analysis populations that will be used in the subsequent review are as follows and enumerated in Table 53:

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

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.

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.

Table 53: Trial 2002 Analysis Groups—Randomized (ITT) Population

	CAZ-AVI + MTZ 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 (74.5)	144 (70.6)

Medical Officer comment: As with Trial 2001, observed differences and analyses with 95% CI are presented only for descriptive purposes and hypothesis generation. Imbalance of numbers of subjects included in ME analysis populations between treatment arms indicates likelihood of the introduction of a number of potential post-randomization biases; therefore, analyses for this trial will be focused the mMITT population.

Approximately half of the subjects enrolled (49 [48.5%] in the CAZ-AVI + MTZ 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.

Table 54: Primary Diagnosis and Surgical Intervention by Treatment Group—mMITT Population

Primary Diagnosis/ Surgical Intervention	Site of Origin	CAZ-AVI + MTZ (N = 85)	Meropenem (N = 89)	Total (N = 174)
Anatomic Site of Origin of Current Infection [a]	Stomach/Duodenum	23 (27.1)	18 (20.2)	41 (23.6)
	Gall Bladder	4 (4.7)	9 (10.1)	13 (7.5)
	Small Bowel	4 (4.7)	12 (13.5)	16 (9.2)
	Appendix	41 (48.2)	43 (48.3)	84 (48.3)
	Colon	12 (14.1)	5 (5.6)	17 (9.8)
	Parenchymal (liver)	1 (1.2)	1 (1.1)	2 (1.1)
	Other	0	1 (1.1)	1 (0.6)
Infection Process [a]	Single Abscess	21 (24.7)	19 (21.3)	40 (23.0)
	Multiple Abscess	2 (2.4)	4 (4.5)	6 (3.4)
	Localized Peritonitis	32 (37.6)	38 (42.7)	70 (40.2)
	Generalized Peritonitis	39 (45.9)	39 (43.8)	78 (44.8)
	Visceral Perforation	37 (43.5)	36 (40.4)	73 (42.0)
Type of Procedure	Open Laparotomy	76 (89.4)	80 (89.9)	156 (89.7)
	Laparoscopic Procedure	8 (9.4)	9 (10.1)	17 (9.8)
	Percutaneous Drainage	1 (1.2)	0	1 (0.6)

Source: Table 2.2.1.3.2–1., Sponsor's ISE for cIAI.

[a] A subject may have had the origin of current infection in more than 1 anatomical site and more than 1 infection process recorded.

Subjects were stratified by APACHE II score at baseline. Descriptive statistics, as well as breakdown of each treatment arms by stratum and quartiles, are summarized in Table 55.

Table 55: Baseline APACHE II Scores—mMITT Population

	CAZ-AVI + MTZ (N = 85)	Meropenem (N = 89)	Total (N = 174)
APACHE II Score Stratum, n (%) [a]			
≤ 10	71 (83.5)	73 (82.0)	144 (82.8)
> 10 and ≤ 25	14 (16.5)	16 (18.0)	30 (17.2)
APACHE II Scores, n (%) [a]			
0 - 5	42 (49.4)	48 (53.9)	90 (51.7)
6 - 10	29 (34.1)	25 (28.1)	54 (31.0)
11 - 15	10 (11.8)	15 (16.9)	25 (14.4)
16 - 19	4 (4.7)	1 (1.1)	5 (2.9)
20 - 25	0 (0.0)	0 (0.0)	0 (0.0)
APACHE II Scores			
n	85	89	174
Mean	6.5	5.9	6.2
SD	4.00	4.08	4.04
Median	6.0	5.0	5.0
Min-Max	0-18	0-16	0-18

Source: Table 2.2.1.3.1–1. Sponsor's ISE for cIAI.

[a] Percentages are calculated using the number of patients with non-missing data in the mMITT population as the denominator.

Prior and Concomitant Antibacterial Therapy

Approximately half of each treatment group in the mMITT population received less than 24 hours of protocol-allowed prior antibiotic therapy. Metronidazole and third-generation cephalosporins were the most common. Four subjects (Subject ID 40005, 67001, 80002, and 80004, each in the CAZAVI + MTZ group) received >24 hours of prior antibiotics. Each subject had failed prior antibiotic therapy and met criteria for enrollment in the study. Of the remaining subjects, 41 (48.2%) and 44 (49.4%) in the CAZAVI + MTZ and meropenem groups, respectively, received only one dose of an antibiotic treatment regimen. Twenty-six (30.6%) and 16 (18.0%) in the CAZAVI + MTZ and meropenem groups, respectively, received multiple prior antibacterial medications.

Approximately 15% of subjects in the mMITT population in each treatment group received concomitant systemic antibacterial therapy. The most commonly administered concomitant antibacterial agents were metronidazole, ciprofloxacin, vancomycin, and linezolid. Five subjects received concomitant vancomycin (3 in CAZAVI + MTZ group and 2 in the meropenem group), and 5 subjects received concomitant linezolid (3 in CAZAVI + MTZ group and 2 in meropenem group). In the CAZAVI + MTZ group, the subjects who received vancomycin either discontinued from study therapy, or had either MRSA or enterococci identified at baseline.

6.2.4 Analysis of Primary Endpoints

The protocol-specified primary endpoint was the clinical response in the ME Population at TOC/EFU (2 weeks post-therapy). Investigator-determined and Sponsor-verified outcomes were also reported. In the Applicant's primary analysis, 68/101 (67%) subjects in the CAZ-AVI + MTZ 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 + MTZ group and 93.4% (71/76) in the meropenem group (see Table 56). 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 56: Clinical Response at TOC/EFU—ME population

	CAZ-AVI + MTZ 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	6 (8.8)	5 (6.6)	

Medical Officer comment: The ME population excludes subjects based on post-randomization criteria that could potentially introduce bias, whereas an analysis based on the mMITT population helps to preserve the effect of randomization. As discussed at the Pre-NDA meeting, and similar to the rationale provided for Trial 2001, the primary efficacy analysis in this review

will focus the on clinical response at the TOC visit 2 weeks post-therapy as performed in the mMITT population. Ideally, however, the TOC should be based on a fixed timepoint from randomization, because length of treatment may vary depending on the time needed for clinical response. Clinical and microbiological responses are also provided by visit (EOIV, TOC and LFU) as secondary endpoints.

Within the mMITT, the Sponsor-verified favorable clinical response was achieved in 70/85 (82.4%) in the CAZ-AVI group and 79/89 (88.8%) in the meropenem group with a difference in clinical response of -6.4% (95% CI: -18.0, 5.2) (Table 57).

Table 57: Clinical Response at TOC/EFU—mMITT Population

	CAZ-AVI + MTZ 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/Indeterminate	15 (17.7)	10 (11.2)	

Medical Officer comment: The 82.4% sponsor-verified response rate in the CAZ-AVI + MTZ group is bounded by a 95% CI of (73.7%, 91.0%). For reference, in the FDA Guidance for cIAI[Error! Bookmark not defined.] a meta-analysis was conducted to estimate the expected rate of clinical success for patients with cIAI treated with an antibacterial drug. Based on recently conducted active-controlled clinical trials, for clinical cure at Day 28, the point estimate was 81.7% (95% CI: 78.8%, 84.3%).

Another meta-analysis of placebo/no treatment trials for prophylaxis in cIAI patients found a 60.8% success rate (95% CI: 56.6%, 64.9%). The lower limit of the 95% CI in the CAZ-AVI group is 8.8% greater than the upper limit of untreated group, but any comparison with this historical estimate of should also be interpreted with caution.

Subjects in the mMITT Population who were clinical failures at TOC are listed in Table 58. Reasons for clinical failure or indeterminate clinical response were similar between treatment groups. Of note, 4 out of the 7 failures in the CAZ-AV + MTZI group had polymicrobial cIAI that included enterococcal spp. or anaerobes, which are not target organisms for CAZ-AVI. Five subjects in the CAZ-AVI + MTZ group and 3 subjects in the meropenem group had missing assessments at the TOC and were therefore given indeterminate clinical responses.

Table 58: Reasons for Clinical Failure at TOC—mMITT Population

Subject	Age	APACHE II Score	Site of Infection	Days on Therapy	Baseline Pathogen(s)	Reason for Failure
CAZ-AVI + MTZ						
12006	62	10	Appendix	3	*C. amalonaticus, E. coli, K. pneumoniae*	Persisting or recurrent cIAI
12007	49	8	Appendix	7	*B. fragilis, E. coli*	Post-surgical wound infections
13001	61	9	Colon	10	*B. fragilis*	Treatment with additional antibiotics
52005	30	6	Gall bladder	11	*E. coli*	Treatment with additional antibiotics for ongoing cIAI symptoms
64012	52	8	Stomach	14	*E. faecium, E. coli*	Persisting or recurrent cIAI documented at re-intervention
67001	40	5	Stomach	14	*E. coli*	Treatment with additional antibiotics for ongoing cIAI symptoms
73001	33	2	Appendix	5	*B. fragilis, E. coli*	Persisting or recurrent infection within the abdomen
Meropenem						
23004	82	9	Small bowel	5	*E. aerogenes*	Persisting or recurrent cIAI
41003	39	1	Appendix	5	*E. coli*	Persisting or recurrent infection within the abdomen
42007	69	9	Colon	6	*E. coli*	Treatment with additional antibiotics
55001	26	2	Appendix	10	*E. coli*	Persisting or recurrent cIAI
64005	20	2	Appendix	13	*E. coli*	Treatment with additional antibiotics

Source: Table 2.2.1.6.1–2. Sponsor's ISE for cIAI.

6.2.5 Analysis of Secondary Endpoints

Additional protocol-specified endpoints included the following:

- Clinical response in the ME population at EOIV and at the LFU
- Clinical response in the mMITT population at EOIV, TOC, and at the LFU.
- Microbiological response in the mMITT population at EOIV, TOC, and at LFU.

Summaries of each of these analyses are presented in Table 59, Table 60, and Table 61, respectively.

Table 59: Sponsor-Verified Clinical Response by Visit and Treatment Group—ME Population

Visit Outcome	CAZ-AVI + MTZ (N=68) n (%)	Meropenem (N=76) n (%)
EOIV		
Clinical Cure	66 (97.1)	74 (97.4)
Clinical Failure	2 (2.9)	2 (2.6)
TOC		
Clinical Cure	62 (91.2)	71 (93.4)
Clinical Failure	6 (8.8)	5 (6.6)
LFU		
Clinical Cure	62 (91.2)	71 (93.4)
Clinical Failure	6 (8.8)	5 (6.6)

Source: Adapted from Table 2.1.1.1.3, Sponsor's ISE, vol. 2 for cIAI

Table 60: Sponsor-Verified Clinical Response by Visit and Treatment Group—mMITT Population

Visit Outcome	CAZ-AVI + MTZ (N=85) n (%)	Meropenem (N=89) n (%)
EOIV		
Clinical Cure	78 (91.8)	81 (91.0)
Clinical Failure	3 (3.5)	2 (2.2)
Indeterminate	4 (4.7)	6 (6.7)
TOC		
Clinical Cure	70 (82.4)	79 (88.8)
Clinical Failure	7 (8.2)	5 (5.6)
Indeterminate	8 (9.4)	5 (5.6)
LFU		
Clinical Cure	71 (83.5)	77 (86.5)
Clinical Failure	7 (8.2)	6 (6.7)
Indeterminate	7 (8.2)	6 (6.7)

Source: Adapted from Tables 2.2.1.6.1–1 and 2.2.1.6.2.2–1, Sponsor's ISE for cIAI

Table 61: By-Pathogen Microbiological Response—mMITT Population

	CAZ-AVI + MTZ N = 85 n/N1 (%)	Meropenem N = 89 n/N1 (%)
Gram Negative Aerobic Pathogens	**59/73 (80.8)**	**68/78 (87.2)**
Enterobacteriaceae	**57/70 (81.4)**	**64/74 (86.5)**
Citrobacter amalonaticus	0/1	0/0
Enterobacter cloacae	1/1	4/5
Escherichia coli	**49/60 (81.7)**	**55/62 (88.7)**
Escherichia hermannii	0/1	0/0
Klebsiella pneumoniae	**6/8 (75.0)**	**11/13 (84.6)**
Klebsiella oxytoca	2/2	2/2
Proteus mirabilis	1/2	1/1
Providencia stuartii	1/1	0/0
Gram negative aerobes other than Enterobacteriaceae	**9/10 (90.0)**	**10/10 (100.0)**
Acinetobacter baumannii	1/1	2/2
Campylobacter gracilis	0/1	0/0
Pseudomonas aeruginosa	**6/6 (100.0)**	**5/5 (100.0)**
Pseudomonas species	1/1	0/0
Pseudomonas stutzeri	1/1	0/0
Stenotrophomonas maltophilia	1/1	0/0
Gram Positive Aerobic Pathogens	**21/23 (91.3)**	**18/18 (100.0)**
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
Anaerobic Pathogens	**10/16 (62.5)**	**10/12 (83.3)**
Bacteroides caccae	2/2	0/1
Bacteroides distasonis	1/1	0/0
Bacteroides eggerthii	1/1	0/0
Bacteroides fragilis	3/7	3/4
Bacteroides thetaiotaomicron	1/2	2/3
Bacteroides uniformis	2/2	1/1
Clostridium clostridioforme	1/2	1/1
Clostridium perfringens	2/2	0/0
Clostridium ramosum	3/3	1/1
Finegoldia magna	1/1	0/0
Fusobacterium necrophorum	0/1	0/0
Fusobacterium varium	1/1	0/0
Peptostreptococcus micros	1/1	1/1
Peptostreptococcus prevotii	0/1	1/1
Prevotella intermedia	1/1	0/0
Prevotella melaninogenica	0/1	0/0

Source: Table 2.2.3.1.5 from the Sponsor's ISE vol. 2 for cIAI. Pathogens listed include only intra-abdominal and blood isolates that were identified in the CAZ-AVI + MTZ group. Percentages are calculated using the number of patients with an assessment with a given baseline pathogen (N1) in the mMITT population as the denominator. Patients who have more than one baseline pathogen are counted only once for each baseline pathogen isolated.

More than a third (36.8%) of the subjects in the mMITT population had polymicrobial infections (64/174). The most common gram-negative pathogens identified were *E. coli, K. pneumoniae, and P. aeruginosa* (in bold type, Table 61). The microbiological response rate was favorable for 49/60 (81.7%) of subjects with *E. coli* isolates in the CAZ-AVI + MTZ group and 55/62 (88.7%) in meropenem group. For all gram-negative aerobic isolates, favorable responses were seen in 80.8% of the CAZ-AVI + MTZ group (59/73) and 87.2% in the meropenem group (68/78).

6.2.6 Other Endpoints

For exploratory purposes, emergent infections (i.e., superinfections or new infections) and mortality were considered as additional endpoints. A new infection was defined as isolation of a new pathogen other than the original baseline pathogen from intra-abdominal culture, which was accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy, at any time after EOT. No subject in either treatment group developed a new infection over the course of the study.

Superinfection was defined as isolation of a new pathogen other than the original baseline pathogen from intra-abdominal culture, which was accompanied by signs and symptoms of infection requiring alternative antimicrobial therapy, during study drug administration (up to and including EOT). In the mMITT Population, 1 subject in the CAZ-AVI + MTZ group was identified in the clinical database as having a superinfection:

> Subject 64012 (CAZ-AVI + MTZ group) was a 52-year-old male with a duodenal perforation and generalized peritonitis at baseline. The subject underwent open laparotomy; the perforation was repaired and associated intestinal adhesions were released. Intra-abdominal cultures were positive for *E. coli* and *E. faecium*. On study Day (b) (6) (of (b) (6) total days of study drug), the subject underwent emergency laparotomy for a new pyloric perforation and repeated intra-abdominal cultures were positive for *E. faecalis*. The *E. faecalis* was considered a superinfection, and he was considered a clinical failure due (Table 58).

One subject in the meropenem group had an apparent superinfection based on clinical details available in an SAE narrative; however, no superinfection pathogen (i.e., *E. faecium*) was captured for this subject in the clinical database:

> Subject 23004 (meropenem) was an 82-year-old female with an intra-abdominal abscess at Baseline. Surgery revealed an inter-intestinal abscess with adherent small bowel loops. Culture of the abscess cavity grew *E. aerogenes*; blood cultures were negative. On Study Day (b) (6) a small bowel leakage occurred, and repeated surgery was performed; culture of lavage fluid grew *E. faecium*. On Study Day (b) (6) the subject died due to secondary diffuse peritonitis. Clinical response at TOC was determined to be failure due to persistent infection documented by a second surgery (Table 58).

Five subjects (3 in the CAZ-AVI + MTZ group and 2 in the meropenem group) died during the study. One subject (Subject 32001) died after being withdrawn from the study on Day (b) (6). Additional safety reviews of the deaths are described in Section 7.3.1. In the mMITT Population,

although no subjects were determined by the Investigator to have "death" cited as the reason for clinical failure, TOC assessments were missing for most of the subjects. For the two subjects who died and were also considered failures (Subject 23004 in the meropenem group and Subject 67001 in the CAZ-AVI + MTZ group), progression of the index infection was likely to be contributory to the death.

Table 62: Clinical Outcomes for Subjects Who Died in Trial 2002—mMITT Population

ID	Treatment	Clinical Response	Duration of IV Therapy	Comment
23004	Meropenem	Failure	(b) (6) days	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	Indeterminate	(b) (6) doses	54-year-old male with perforation of the sigmoid colon, multiple abdominal and pelvic abscesses. Discontinued from study by the investigator on Day (b) (6) due to septic shock.
42005	CAZ-AVI + MTZ	Missing	(b) (6) days	79-year-old male with acute appendicitis and peri-appendiceal abscess. Deterioration due to pneumonia with pleural effusion.
63006	Meropenem	Missing	(b) (6) days	59-year-old male with ileal perforation and peritonitis. Sudden cardiorespiratory arrest on Day (b) (6).
67001	CAZ-AVI + MTZ	Failure	(b) (6) days	40-year-old male with acute pancreatitis and intestinal perforation.
72003	CAZ-AVI + MTZ	Missing	(b) (6) doses	55-year-old male with perforated gastric ulcer and peritonitis, abdominal aortic aneurysm and occluded bilateral femoral arteries, status post embolectomy.

6.2.7 Subpopulations

Analyses of clinical outcomes were reported based on demographic subpopulations. The numbers within each subgroup were small and varied within each subgoup. No Native Hawaiian, Pacific Islander, Black or African American subjects were included. Table 63 summarizes Sponsor-verified outcome at TOC by gender, age and race in the mMITT population.

Table 63: Summary of Clinical Outcome at TOC by Demographic Group—mMITT Population

Demographic Subgroup	CAZ-AVI + MTZ (N = 85) n/N (%)	Meropenem (N = 89) n/N (%)
Overall	70/85 (82.4)	79/89 (88.9)
Gender		
Male	48/60 (80.0)	63/71 (88.7)
Female	22/25 (88.0)	16/18 (88.9)
Age Category		
18 to 64	67/81 (82.7)	69/77 (89.6)
≥65	3/4 (75.0)	10/12 (83.3)
≥75	0/1 (0.0)	1/2 (50.0)
Race		
White or Caucasian	37/50 (74.0)	53/59 (89.8)
Asian	21/23 (91.3)	18/21 (85.7)
American Indian or Alaskan Native	1/1 (100.0)	0/0
Other	11/11 (100.0)	8/9 (88.9)
Ethnicity		
Hispanic or Latino	1/3 (33.3)	2/2 (100.0)
Non-Hispanic or Latino	69/82 (84.1)	77/87 (88.5)
Region		
US	3/9 (33.3)	5/5 (100.0)
Rest of World	67/76 (88.2)	74/84 (88.1)

Medical Officer comment: Numbers of subject in each demographic category were small. Interpretation of any imbalance between outcomes in subgroups is limited.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Because the dose used in Trial 2001 was 25% of the dose used in Trial 2002 and the currently proposed recommended dose for labeling, and because cIAI is a more conservative target than cUTI, clinical outcomes were assessed by MIC to CAZ-AVI (in combination with PK/PD target attainment analysis) for determination of breakpoint susceptibility criteria. The favorable Sponsor-verified clinical and microbiological response rates for CAZ-AVI as a function of MIC to ceftazidime-avibactam against all Enterobacteriaceae and *P. aeruginosa* were collected from each treatment group in the mMITT population are shown in Table 64.

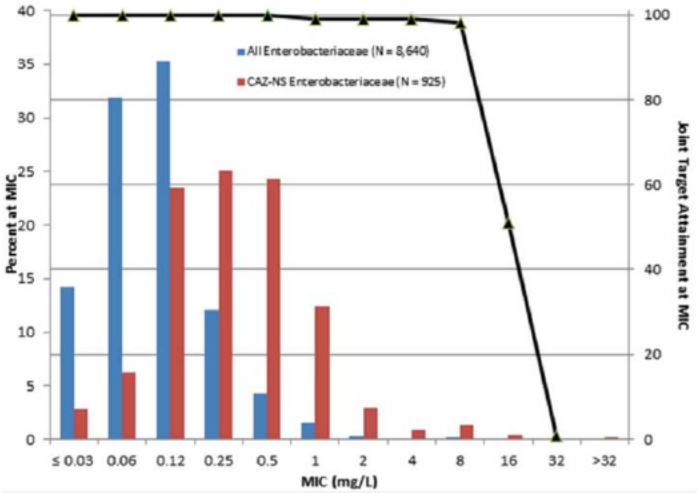
Table 64: Favorable Sponsor-Verified Clinical Responses for CAZ-AVI against All Enterobacteriaceae and *Pseudomonas aeruginosa*—Trial 2002, mMITT Population

Ceftazidime-avibactam MIC (mg/L)	Favorable sponsor-verified clinical response n/N (%)
Enterobacteriaceae	
≤ 0.03	10/12 (83.3)
0.06	18/21 (85.7)
0.12	15/20 (75.0)
0.25	8/9 (88.9)
0.5	2/2 (100.0)
1	1/1 (100.0)
2	2/3 (66.7)
8	1/1 (100.0)
> 32	0/1 (0.0)
Pseudomonas aeruginosa	
8	1/1 (100.0)
2	3/3 (100.0)
4	1/1 (100.0)
> 32	1/1 (100.0)

Source: Tables 4.5.1.1.6.1–1 and Table 4.5.1.1.6.3.1–1 from the Sponsor's Summary of Clinical Pharmacology.

Percentages of simulated patients with normal renal function achieving 50% *f*T > MIC for ceftazidime and 50% *f*T > C_T of 1 mg/L avibactam following IV administration of 2000 mg/500 mg CAZ-AVI q8h (2 hour infusion) were overlaid on a histogram of MIC distributions for Enterobacteriaceae collected during the 2012 US surveillance program. The joint PK/PD target attainment analysis is presented in Figure 5.

Figure 5: Probability of Joint Target Attainment by MIC for Enterobacteriaceae



Source: Figure 4.6.2.5.2–1. Sponsor's Summary of Clinical Pharmacology.

Medical Officer comment: No clear trend in clinical or microbiological outcomes was observed in clinical trials with CAZ-AVI over the MIC range that would confirm choice of susceptibility breakpoints. Based on PTA, using a conservative taget at the MIC of 16 mg/L, only 50.8% of simulated cIAI patients achieved target (Table 16 and Figure 5). Additionally, since there are no planned dose adjustments, whereby a higher dose of CAZ-AVI may be used safely, the criteria for "intermediate" were omitted (Table 65). Taken together, these analyses support a "susceptible" breakpoint of ≤ 8 mg/L. Please also refer to the reviews by Clinical Pharmacology reviewer, Dr. Jang and Clinical Microbiology reviewer, Dr. Goodwin.

Table 65: Susceptibility Interpretive Criteria for Ceftazidime/Avibactam

Pathogen	***Minimum Inhibitory Concentration (mg/L)***		***Disk Diffusion Zone Diameter (mm)***	
	S	*R*	*S*	*R*
Enterobacteriaceae	≤ 8/4	≥ 16/4	≥ 21	≤ 20
Pseudomonas aeruginosa	≤ 8/4	≥ 16/4	≥ 18	≤ 17

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No subject in the mMITT Population had a microbiological outcome of persistence associated with post-baseline acquisition of resistance.

6.2.10 Additional Efficacy Issues/Analyses

In the subgroup of subjects with infections caused by CAZ-NS pathogens (Table 66), the Sponsor-verified favorable clinical response is 27/30 (90.0%) in the CAZ-AVI + MTZ 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 57); while in the subgroup of subjects infected with CAZ-NS pathogens, CAZ-AVI + MTZ has a numerically higher treatment response than meropenem (Table 66). It is not clear why the CAZ-AVI +MTZ response rate is lower than meropenem in the mMITT population.

Table 66: Clinical Response at TOC/EFU—mMITT Population, Subjects with a CAZ-NS Pathogen

	CAZ-AVI + MTZ 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/Indeterminate	3 (10.0)	4 (17.4)	

Among subjects assigned to CAZ-AVI +MTZ with a CAZ-susceptible pathogen, 43 of 55 (78.2%) had a Sponsor-verified favorable clinical response (Table 67). 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%, highlighted in Table 67). This may be considered an internal control group or putative estimate for inadequate treatment. The difference in response rate between those given CAZ-AVI + MTZ (82.4% in mMITT population, highlighted in Table 57) 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 67: Clinical Response at TOC/EFU by Treatment Group and Susceptibility of Pathogen to Ceftazidime or Meropenem—mMITT population

	CAZ-AVI + MTZ N = 85 n (%)	**Meropenem N = 89 n (%)**
Susceptible to	**Ceftazidime (N1=55)**	**Meropenem (N1=85)**
Cure	43 (78.2)	76 (89.4)
Failure/Indeterminate	12 (21.8)	9 (10.6)
Nonsusceptible to	**Ceftazidime (N1=30)**	**Meropenem (N1=4)**
Cure	27 (90.0)	3 (75.0)
Failure/Indeterminate	3 (10.0)	1 (25.0)

Medical Officer comment: The point estimate for the cure rate of CAZ-AVI+MTZ in the CAZ-NS subgroup was bounded by a 95% CI with a lower bound of 77.6%. This is 12.7% higher than the upper bound of the point estimate for untreated controls[Error! Bookmark not defined.], which indicates a treatment effect may have been demonstrated. Drawing conclusions from this post hoc inference testing, however, remains problematic. Findings for the cure rates seemed paradoxical (rates were lower in the CAZ-S subpopulation than the overall or even CAZ-NS population), which may have been due to chance variation within a small trial (especially given the variability of surgical intervention), as well as the gap left by subjects who had missing or indeterminate clinical outcomes. Additionally, note that the putative estimate for inadequate treatment based on the meropenem-NS subgroup (75.0%) is higher than the estimated placebo rate derived from a meta-analysis of untreated controls, and similar to the CAZ-S population. This leaves several uncertainties in the interpretation of these comparisons.

Favorable microbiological response by baseline pathogen at TOC is shown in Table 68. *E. coli* was eradicated in 20/22 (90.1%) cases in the CAZ-AVI + MTZ group and 15/17 (93.8%) cases in the meropenem group at TOC. Eradication rate in either subgroup is relatively high.

Table 68: By-Pathogen Sponsor-Verified Clinical Response at TOC—mMITT Population, Subjects with a CAZ-NS Pathogen

	CAZ-AVI + MTZ (N = 30) n/N1	Meropenem (N = 23) n/N1
Enterobacteriaceae	25/28 (89.3)	18/22 (81.8)
Escherichia coli	20/22 (90.9)	15/17 (88.2)
Klebsiella pneumoniae	3/4 (75.0)	3/5 (60.0)
Proteus mirabilis	1/1 (100.0)	0/0 (0.0)
Providencia stuartii	1/1(100.0)	0/0 (0.0)
Citrobacter braakii	0/0 (0.0)	1/1 (100.0)
Enterobacter cloacae	0/0 (0.0)	0/1 (0.0)
Gram-negative aerobes other than Enterobacteriaceae	2/2 (100.0)	2/2 (100.0)
Pseudomonas aeruginosa	1/1 (100.0)	1/1 (100.0)
Acinetobacter baumannii	1/1 (100.0)	1/1 (100.0)

Source: Table 2.2.1.6.2.7.1-2, from the Sponsor's ISE vol 1 for cIAI. %s are calculated using the number of patients with an assessment with a given baseline pathogen (N1) in the mMITT population as the denominator. A single patient may have had multiple isolates.

In the following table, Table 69, clinical outcomes at TOC are summarized in subgroups of subjects by baseline MIC to ceftazidime.

Table 69: Favorable Sponsor-Verified Clinical Outcome at TOC by Treatment Group and Baseline Pathogen MIC to Ceftazidime (Intra-Abdominal and Blood Isolates)—mMITT Population

Pathogen Ceftazidime MIC (mg/L)	CAZ-AVI + MTZ (N=85) n/N (%)	Meropenem (N=89) n/N (%)
Enterobacteriaceae		
Isolated	70	74
Tested	70	73
0.06	5/6 (83.3)	8/9 (88.9)
0.12	14/20 (70.0)	22/27 (81.5)
0.25	9/10 (90.0)	13/13 (100)
0.5	3/3 (100.0)	0/0
1	0/2	1/1 (100)
2	1/1 (100)	0/0
8	0/0	1/1 (100)
16	4/5 (80.0)	2/2 (100)
32	8/8 (100)	5/5 (100)
>32	13/15 (86.7)	11/15 (73.3)
Pseudomonas aeruginosa		
2	4/4 (100)	3/3 (100)
4	0/0	1/1 (100)
8	1/1 (100.0)	0/0
32	0/0	1/1 (100)
>32	1/1 (100)	0/0

Source: Table 2.2.5.3.7 from the Sponsor's Summary of Clinical Pharmacology. For subjects with the same pathogen isolated more than once, the pathogen with the highest MIC is shown. N = Number of subjects in the mMITT Population. N1 = Number of Subjects with the specified organism at the given MIC level. n = Number of subjects with favorable sponsor-verified clinical response for the organism at the given MIC level. Percentages are calculated as 100 x (n/N1).

The most common class of any category of β-lactamase gene in the mMITT population was ESBL (44/174 [25.3%] patients), and *bla*$_{CTX-M-15}$ in combination with other genes was the most common β-lactamase gene (36/174 [20.7%] patients. Table 70 summarizes clinical outcomes at TOC by β-lactamase genotype. No outcomes were described for pathogens with KPC or Class B (metallo-β-lactamase) genotypes. Only one pathogen in the CAZ-AVI + MTZ arm had a Class D (OXA-51) genotype.

Table 70: Summary of Clinical Outcome at TOC by Resistance Mechanism—ME Population, Subjects with a Pathogen Possessing Any Category I β-lactamase Gene

β-lactamase group	Genotype	CAZ-AVI +MTZ (N=68) n/m (%)	Meropenem (N=76) n/m (%)
ESBL		18/20 (90.0)	15/16 (93.8)
	CTX-M-15 alone	1/1 (100)	2/2 (100)
	CTX-M-15 in combination	14/16 (87.5)	12/13 (92.3)
	PER-1 in combination	1/1 (100)	0/0
	SHV-12 alone	0/0	1/1 (100)
	SHV-12 in combination	3/3 (100)	0/1 (0.0)
	SHV-2 in combination	0/1 (0.0)	0/0
	SHV-31 in combination	0/0	1/1 (100)
	SHV-5 in combination	0/0	1/1 (100)
Class C		5/6 (83.3)	3/4 (75.0)
	ACC-4 in combination	2/2 (100)	0/0
	CMY-2 in combination	0/0	0/1 (0.0)
	CMY-42 in combination	3/4 (75.0)	2/2 (100)
	CMY-6 alone	0/0	1/1 (100)
Class D		1/1 (100)	2/2 (100)
	OXA-10 in combination	0/0	1/1 (100)
	OXA-23 in combination	0/0	1/1 (100)
	OXA-4 in combination	0/0	1/1 (100)
	OXA-51 in combination	1/1 (100)	1/1 (100)

Source: Table 11.2.2.1, Sponsor's CSR for Trial 2002, Addendum 1. A subject can have more than one category of beta-lactamase.
n = Number of patients in subgroup with clinical cure. m = Number of patients in subgroup.

Subjects were stratified at enrollment based on APACHE II scores. Summary of clinical responses were summarized by quartiles and stratum (Table 71). Small numbers in each category limited interpretation between treatment groups.

Table 71: Clinical Response at TOC/EFU by APACHE II Score, Stratum—mMITT Population

	CAZ-AVI n (%)	Meropenem n (%)
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)

Bacteremia was uncommon, and rates of baseline bacteremia by pathogen were similar between the two treatment groups. Overall, 13 subjects (7.5%) had bacteremia at baseline. There were 7 (8.2%) in the CAZ-AVI + MTZ group with baseline bacteremia and 6 (6.7%) in the meropenem group. In the CAZ-AVI + MTZ group, there were 3 gram-negative isolates: 2 *E. coli* and 1 *Pseudomonas stutzeri*. In the meropenem group, there were 4 *E. coli* and 1 *Acinetobacter baumannii*. For both treatment groups, all subjects were considered clinical cures at TOC. None of the blood isolates were CAZ-NS.

6.3 Indication: Aerobic Gram-Negative Infections with Limited or No Alternative Treatment Options including HABP/VABP and Bacteremia

(b) (4)

requested indication for HABP/VABP and bacteremia is not accompanied by any clinical data from a well-controlled trial designed for these indications. For the purposes of this review, rather than evaluating efficacy for the indication requested, the interim data presented from the Resistant Pathogen Study will be covered separately in this section as supportive descriptive evidence for the requested indications of cIAI and cUTI. Please also refer to Dr. Gamalo's statistical review for exploration into comparisons with historical estimates of treatment effect for ceftazidime alone for cUTI and cIAI. These analyses, however, will not be discussed in detail in this review due to the limitations of comparability between patient populations, dosage regimens used and trial design.

Study D4280C00006

Primary objective

- To estimate the per-patient clinical response to CAZ-AVI and BAT at TOC in the treatment of selected serious infections caused by ceftazidime-resistant gram-negative pathogens.

Secondary objectives

- To further evaluate the clinical response to CAZ-AVI and BAT at different visits and in patient subgroups (including entry diagnosis, pathogen, resistance mechanism, and previously failed treatment class).
- To estimate the microbiological response to CAZ-AVI and BAT in the treatment of selected serious infections caused by ceftazidime-resistant gram-negative pathogens.
- To evaluate the reasons for treatment change and/or discontinuation for CAZ-AVI and BAT
- To estimate the 28-day, all-cause mortality among patients treated with CAZ-AVI and BAT
- To evaluate the safety and tolerability profile of CAZ-AVI and BAT for the treatment of selected serious infections caused by ceftazidime-resistant gram-negative pathogens
- To evaluate the pharmacokinetics (PK) of the individual components of CAZ-AVI in this population with selected serious infections, and to characterize the relationship between the PK and clinical and microbiological response for CAZ-AVI

Medical Officer comment: This study was designed to supplement the Phase 3 program and obtain further information regarding resistant gram-negative bacterial pathogens that may not have been included in that population because they were resistant to the chosen comparator or in patients with multiple comorbidities.

6.3.1 Methods

This is a prospective, open-label, randomized, multicenter, study to evaluate the efficacy, safety, and tolerability of CAZ-AVI and BAT in the treatment of hospitalized adults with cIAIs and cUTIs caused by ceftazidime-NS gram-negative pathogens (ceftazidime resistance is defined as those bacterial isolates whose susceptibility results are intermediate or resistant using CLSI methodology and isolates that are resistant using EUCAST methodology). Planned enrollment is

for approximately 400 hospitalized adult (≥18 years of age) subjects. Subjects are stratified for entry diagnosis (cIAI and cUTI) and region (North America and Western Europe, Eastern Europe, and the rest of the world), then randomized 1:1 to CAZ-AVI or BAT groups.

Subjects who received appropriate prior empiric antibacterial therapy (based on microbiological susceptibility test results) for a CAZ-R pathogen must meet at least 1 of the following criteria:

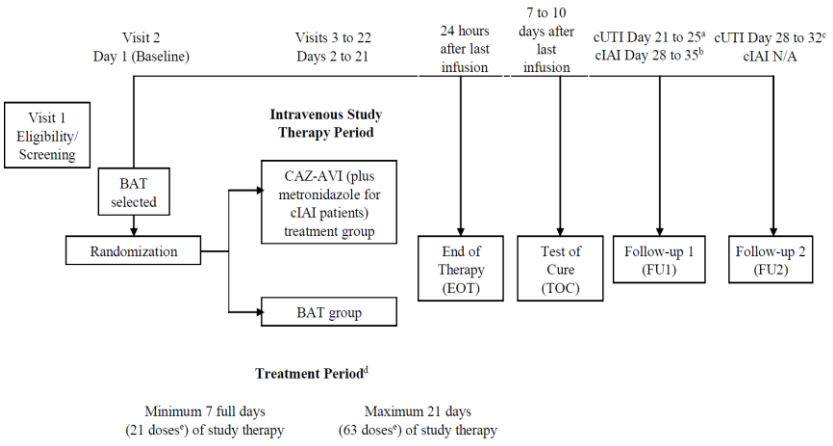
a. Worsening of objective symptoms or signs of infection after at least 48 hours of appropriate therapy
b. Lack of improvement of objective symptoms or signs of infection after at least 72 hours of appropriate therapy
c. Persistent positive cultures from the site of infection or from blood

Patients with infections unlikely to respond to CAZ-AVI (e.g., *Acinetobacter* spp., *Stenotrophomonas* spp.), or patients who have an estimated CrCL < 6 mL/min were excluded.

The dosing regimens for CAZ-AVI, including adjustments for renal impairment, are equivalent to proposed doses in Table 1. The preferred BAT options are meropenem, imipenem, doripenem, tigecycline, and colistin. The addition of metronidazole is encouraged with colistin if anaerobic coverage is needed for cIAI. The duration of treatment with study medication is 5 to 21 days with no oral switch. After 5 full days of study therapy and at the discretion of the Investigator, all study therapies may then be discontinued.

The study flow chart is shown in Figure 6. An overall clinical assessment, vital sign measurement, and assessment of infection-related signs and symptoms will be performed at Day 1 (Baseline), daily during treatment with study therapy, and at the EOT, TOC, FU1, and FU2 visits. For cIAI patients, clinical signs and symptoms will include abdominal signs and symptoms plus abdominal and wound examinations. For cUTI, clinical signs and symptoms include fever or chills, flank pain, costovertebral angle tenderness, dysuria, urgency, frequency, incontinence, suprapubic pain, and nausea or vomiting. Plasma samples for PK sampling will be taken from all patients on Day 3.

Figure 6: Study Design - Resistant Pathogen Study D4280C00006



As of 9 December 2013, 48 subjects were enrolled at sites in 7 countries outside of the US. Sites were selected for reasons that included high incidences of infections caused by CAZ-NS pathogens. Most subjects have been enrolled from sites in Bulgaria and Romania. One subject in the CAZ-AVI group discontinued study drug due to being lost to follow-up.

Clinical endpoints for cUTI were assesses as either cure, failure, and indeterminate and were assessed at EOT, TOC, FU1 and FU2. Microbiological endpoints were either eradication, persistence, and indeterminate, also assesat EOT, TOC, FU1 and FU2 visists are. Microbiological Response at TOC in the mMITT population was determined as either favorable (eradication) or unfavorable (persistence). For cIAI, clinical endpoints were assessed at EOT, TOC, and FU1.

6.3.2 Summary of Preliminary Results

Preliminary results for patients with cUTI are summarized in Table 72. Fifteen (71.4%) of 21 subjects treated with CAZ-AVI for cUTI had favorable microbiological responses, and 19 (90.5%) were clinical cures. In the BAT group, 11 (47.8%) of 23 subjects had favorable microbiological responses, and 18 (78.3%) were clinical cures.

Table 72: Clinical and Microbiological Response at TOC—cUTI Subjects with CAZ-NS Pathogens

	CAZ-AVI (N=21) n (%)	BAT (N=23) n (%)
Microbiological Response		
Eradication	15 (71.4)	11 (47.8)
Persistence	5 (23.8)	12 (52.2)
Indeterminate	1 (4.8)	0
Clinical Response		
Clinical cure	19 (90.5)	18 (78.3)
Clinical failure	1 (4.8)	1 (4.3)
Indeterminate	1 (4.8)	4 (17.4)

Source: Tables 2.2.2.5.1–1 and 2.2.2.5.4–1 in the Sponsor's ISE for cUTI.

One subject with cIAI was treated with CAZ-AVI and was a clinical cure, whereas 1 of 3 subjects treated with BAT was a clinical cure at TOC. Because only 4 subjects had cIAI, results for CAZ-NS infections across both cUTI and cIAI from Trials 2001, Trial 2002 and the Resistant Pathogen Study were pooled.

6.3.3 Analyses of Pooled Results

Table 73 shows the clinical response rates for pooled mMITT populations, including subjects with CAZ-S and CAZ-NS pathogens, from Trial 2001, Trial 2002 and the Resistant Pathogen

Study. Based on simple pooling across indications, the clinical response rate in among CAZ-AVI-treated subjects is 83.0% and the combined comparator response rate is 81.7%. Although the cure rates were numerically higher in the cUTI population, response rates were lower among comparators in the cIAI population. Although CIs are narrower than individual results, indicating greater certainty in the point estimates, they are presented here only for descriptive purposes.

Table 73: Pooled Clinical Response at TOC/EFU from Trial 2001, Trial 2002 and Resistant Pathogen Study (D4280C00006)—mMITT Population

	CAZ-AVI n/N (%)	Comparators n/N (%)	Difference (95% CI)
Pooled cUTI Population			
Clinical Cure	56/67 (83.6)	54/72 (75.0)	8.6 (-6.1, 22.6)
Pooled cIAI Population			
Clinical Cure	71/86 (82.6)	80/92 (87.0)	-4.4 (-16.0, 7.0)
Pooled mMITT Population			
Clinical Cure	127/153 (83.0)	134/164 (81.7)	1.3 (-7.6, 10.1)

The pooled clinical and microbiological responses for ceftazidime-avibactam and comparators against ceftazidime-non-susceptible Enterobacteriaceae identified among subjects with cIAI and cUTI in the Phase 2 and Resistant Pathogen Studies are summarized in Table 74.

Table 74: Summary of Pooled Clinical and Microbiological Outcomes by Pathogens across All Clinical Studies—Subjects with cIAI and cUTI, CAZ-NS Baseline Pathogen

	Overall Favorable Clinical Outcome at TOC (mMITT Population)		Overall Favorable Microbiological Outcome at TOC (mMITT Population)	
	CAZ-AVI ± MTZ n/N (%)	Comparator n/N (%)	CAZ-AVI ± MTZ n/N (%)	Comparator n/N (%)
Enterobacteriaceae	55/63 (87.3)	46/65 (70.8)	49/63 (77.8)	39/65 (60.0)
Citrobacter braakii		1/1 (100.0)		1/1 (100.0)
Citrobacter freundii complex	1/1 (100.0)		1/1 (100.0)	
Enterobacter aerogenes	1/1 (100.0)		1/1 (100.0)	
Enterobacter cloacae	2/2 (100.0)	0/2 (0.0)	1/2 (50.0)	1/2 (50.0)
Escherichia coli	35/41 (85.4)	30/42 (71.4)	33/41 (80.5)	28/42 (66.7)
Klebsiella oxytoca		2/2 (100.0)		1/2 (50.0)
Klebsiella pneumoniae	13/14 (92.9)	14/20 (70.0)	11/14 (78.6)	9/20 (45.0)
Proteus mirabilis	2/3 (66.7)		1/3 (33.3)	
Providencia stuartii	1/1 (100.0)		1/1 (100.0)	
Other gram-negative aerobes				
Pseudomonas aeruginosa	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	1/2 (50.0)

Source: Table 4.6.2.5–2 and 4.6.2.6–2. Sponsor's Summary of Clinical Pharmacology Studies

Medical Officer comment: Pooling observations across trials assume exchangeability of subjects who had similar characteristics and were given comparable care. In this case, analyses are viewed with caution because there are several important characteristics of these trials that differ. For example, the dose used in Trial 2001 was 25% lower from the other two studies, and the Resistant Pathogen Study was open-label, and more likely to enroll higher risk patients.

7 Review of Safety

Safety Summary

The safety review for CAZ-AVI was completed in the context of its potential benefit for the treatment of complicated urinary tract and intra-abdominal infections with an unmet need. 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 subjects). 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). From the analysis of the safety database for the cUTI and cIAI indications, there was adequate clinical experience with CAZ-AVI at the dose and duration proposed for marketing to evaluate its safety profile.

CAZ-AVI appears to have a similar safety profile to that of the active comparators (e.g., imipenem-cilastatin and meropenem), ceftazidime and the cephalosporin drug class, including minor elevations in serum aminotransferase and alkaline phosphatase values, which were generally transient and not associated with symptoms or development of more severe liver injury. Serious adverse events identified as possibly related to CAZ-AVI were acute renal failure, increase in hepatic enzymes, diarrhea, and pruritic rash. The most commonly reported adverse reactions (incidence of > 10% in either indication) were vomiting, nausea, constipation, and anxiety. Adverse reactions that were identified as likely responsive to dose were nausea and vomiting.

Based on prior experience with ceftazidime, serious reactions have been reported, including urticaria, anaphylaxis, angioedema, hyperbilirubinemia, jaundice, myoclonus and status epilepticus. With drugs in the cephalosporin class, other serious reactions include colitis, hepatic dysfunction (including cholestasis), aplastic anemia, hemorrhage, toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycosides or potent diuretics such as furosemide. Abnormal laboratory tests include prolonged prothrombin time, false-positive test for urinary glucose, and pancytopenia. In a review of literature describing ceftazidime, a specific subtype of status epilepticus, non-convulsive status epilepticus (NCSE), was identified as an additional safety concern that was not previously described in labeling for ceftazidime. NCSE refers to a prolonged seizure diagnosed by electroencephalogram (EEG) that manifests primarily as altered consciousness or encephalopathy.

To date, 61 deaths have been reported in the cumulative CAZ-AVI clinical program, including 7 in the Phase 2 studies (4 CAZ-AVI, 3 comparator) and 54 in the ongoing Phase 3 studies (11 comparator, 16 CAZ-AVI and 27 that remain treatment blinded). Based on review of the 12 unblinded narratives provided, each appears to be attributable to underlying comorbidities, treatment failure and/or emergent infection.

In the Phase 1 Clinical Pharmacology studies (reviewed in Section 5.3), there were no SAEs and no deaths. There was one discontinuation of study drug due to a TEAE (urticaria, discussed in Section 5.3.5), which resolved following treatment with an antihistamine. Minor and transient elevations in serum aminotransferase and ALP values were observed in other healthy volunteers who received 5 days of avibactam alone or CAZ-AVI (Study NXL104/1002), and in an ELF study (D4280C00009) following 3 days of CAZ-AVI. In another study (D4280C00010), one subject who received multiple doses avibactam 500 mg avibactam alone had a transient, asymptomatic increase of serum liver enzymes values (AST, ALT, GGT and ALP) on study Day 5 with transaminases exceeding 5× ULN. One study (D4280C00011) was temporarily halted to adjust stopping rules. None of the additional cases, however, were symptomatic, considered potentially clinically significant, or met Hy's criteria. In the Phase 1 studies, the most frequent AEs among subjects receiving avibactam alone were headache (3.4%), diarrhea (2.0%), and application site bruise (2.0%). In the CAZ-AVI only groups, the most frequent AEs were headache (7.9%) and abnormal urine odor (5.2%).

In Trial 2001 for the cUTI indication, a total of 137 subjects were enrolled, with 69 randomized to the CAZ-AVI group and 68 to the imipenem-cilastatin (IMI-CS) group. There was one death, which was reported in the IMI-CS group. Two subjects in the IMI-CS group experienced 2 SAEs, whereas 7 subjects (10.3%) in the CAZ-AVI group experienced 7 SAEs. Diarrhea, accidental overdose and acute renal failure were assessed by the Investigator as likely related to the study drug in the CAZ-AVI group. None of the SAEs reported was experienced by more than one subject. In the CAZ-AVI group, 18 subjects (26.5%) prematurely discontinued study drug compared to 11 (16.4%) in the IMI-CS group; however, most of the discontinuations were due to screening failures. Two (2.9%) of the discontinuations in the CAZ-AVI group were associated with non-fatal SAEs (accidental overdose in one subject and atrial fibrillation in another). There were no TEAEs resulting in discontinuation in the IMI-CS group. The most frequent TEAEs, where incidence was greater in the CAZ-AVI group than IMI-CS, were constipation (10.3%), anxiety (10.3%) and abdominal pain (8.8%). Headache was the most frequent TEAE (20.6%), but was reported more frequently in the IMI-CS group (31.3%).

In Trial 2002 for the cIAI indication, a total of 203 subjects were enrolled, with 101 randomized to receive CAZ-AVI + metronidazole (MTZ) and 102 to receive meropenem. There were 6 deaths, 4 in the CAZ-AVI + MTZ group and 2 in the meropenem group. There were no TEAEs in the CAZ-AVI + MTZ group assessed by the Investigator as related in any of the subjects who of died. The most frequent SAEs were in the Gastrointestinal Disorders and Infections and Infestations SOC, and included intestinal obstruction and pneumonia. Seven subjects (6.9%) in the CAZ-AVI+ MTZ group had 9 non-fatal SAEs. Diarrhea, accidental overdose, and acute renal failure were assessed by the Investigator as likely related to the study drug. Nine subjects in the meropenem group experienced 9 SAEs. No SAE occurred in > 2 subjects in either treatment group. Two AEs (hepatic enzymes increase, which was reported as an SAE, and pruritic rash) were reported in one subject who prematurely discontinued CAZ-AVI + MTZ. Another subject in the CAZ-AVI + MTZ group discontinued therapy during the third dose due to a non-serious

TEAE (generalized rash). The most frequent TEAEs where incidence was greater in the CAZ-AVI +MTZ group than the meropenem group were vomiting (13.9%), nausea (9.9%) and anxiety (5.0%).

Overall, in the Phase 2 clinical program, there were no findings showing trends or safety concerns that indicated CAZ-AVI has an observable effect on hematology or coagulation parameters above that of the comparators. The incidence of a positive Coombs' test was < 10% for both the CAZ-AVI and comparator groups; 7.3% vs 2.4%, respectively in cIAI and 1.9% vs 8.3%, respectively in cUTI. None of these subjects had laboratory evidence of hemolysis or other TEAEs representing hematologic disorders. There were no clinically meaningful changes in vital signs associated with CAZ-AVI. Mean and max changes in QTcF were similar between CAZ-AVI and comparator groups. One in the CAZ-AVI group in Trial 2001 had QTcF values > 500 msec and changes from baseline > 60 msec based on the centrally read ECG values, but no associated cardiac TEAEs were reported.

In the open-label Resistant Pathogen Study (D4280C00006), which enrolled subjects with cIAI or cUTI caused by CAZ-NS pathogens, 8 SAEs 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. Six subjects died (3 in the CAZ-AVI group and 3 in the BAT comparator group). Three subjects discontinued study drug due to a TEAE (1 in the CAZ-AVI group, 2 in the BAT comparator group). The subject in the CAZ-AVI group was reported to have discontinued study drug due to cardio-respiratory arrest, which was also a fatal SAE (likely unrelated to the study drug). For the two subjects in the BAT comparator group, one subject had lobar pneumonia (unrelated) and the other had CDAD (likely related).

The estimated incidences of SAEs from the ongoing Phase 3 cIAI and cUTI studies are similar to those from the completed Phase 2 studies. Within each study, each SAE reported by the investigator as related to the study drug occurred in 1 to 2 subjects. Preferred terms included increased transaminases, drug eruption, hypersensitivity and pyrexia.

The most concerning safety issue requiring additional evaluation is the imbalance in mortality and clinical cure rates comparator in the Phase 3 cIAI trial among subjects with baseline renal impairment (CrCL < 50 mL/min) who were treated with renally-adjusted doses of CAZ-AVI. The proposed recommended dosing regimen includes renal dose adjustments for patients with CrCL < 50 mL/min; however, in Trials 2001 and 2002, subjects with CrCL < 50 were excluded. Although the Applicant's proposed adjustments in response to these findings appear to be adequate (based on PK/PD modeling) and may potentially address the imbalance in this patient population, additional analysis to determine the need for further study will be recommended, because the relationship between drug exposure and treatment response and the adequacy of these adjustments have not yet been established. Addition of a warning to the label instructing prescribers to follow CrCL daily and adjust doses accordingly will also be recommended.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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 75.

Table 75: 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)

A summary of experience from ongoing Phase 1 and Phase 3 studies is summarized in Table 76.

Table 76: Ongoing Phase 1 and Phase 3 Studies

Study ID	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)	—	—	1066
D4280C00002/4 (cUTI)	—	—	903
D4280C00006 (cIAI and cUTI)	113	109	—
D4280C00018 (cIAI)	—	—	250
Total Subjects: Phase 3	113	109	2677
Total	**162**	**113**	**2927**

[a] D4280C00001/5 (cIAI) now completed. Remaining available exposure data from Phase 3 updated as of 15 Jun 2014.

7.1.2 Categorization of Adverse Events

An AE was defined as any unfavorable and unintended sign, symptom, syndrome, or illness that developed or worsened during the period of observation in a clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) were considered to be AEs. No causal relationship with the study drug or with the clinical study itself was implied by the use of the term “adverse event”.

For studies evaluating drug efficacy, worsening of a sign or symptom of the condition under treatment would normally be measured by efficacy parameters. However, if the outcome fulfilled the definition of a SAE, it was recorded as such. A notable exception is that in the ongoing Phase 3 studies death due to progression of the index infection was not considered an SAE.

Surgical procedures themselves were not AEs; they were considered therapeutic measures for conditions that require surgery. The condition for which the surgery was required was considered an AE if it occurred or was detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures were not considered AEs if the condition(s) were known before the start of study treatment. In the latter case, the condition was reported as medical history.

For all safety parameters in all studies, unless otherwise specifically defined, baseline was defined as the last non-missing assessment before the start of study treatment.

Severity was categorized as mild, moderate, or severe. The definitions used in the Phase 2 studies are defined in Table 77.

Table 77: Categorization for Severity Assessments

Mild	Awareness of sign or symptom, but easily tolerated. Not expected to have a clinically significant effect on the subject's overall health and well-being. Not likely to require medical attention.
Moderate	Discomfort enough to cause interference with usual activity or affects clinical status. May require medical intervention.
Severe	Incapacitating or significantly affecting clinical status. Likely requires medical intervention and/or close follow-up.

AEs were initially coded to a system organ class (SOC) and preferred term using different versions of the MedDRA. For the Phase 2 cIAI and cUTI studies, AEs were coded using MedDRA Version 11.1 or higher and Version 8 or higher, respectively. The period of observation for collection of AEs extended from the time the subject gave informed consent until 14 days after EOT.

TEAEs were defined as those events that began or worsened in severity during or after administration of the first dose of study drug through the end of the period of observation for collection of AEs. AEs with no onset times available, but with onset dates equal to the dates of the first doses of study drug, were conservatively counted as treatment emergent unless the AE was considered not treatment emergent in the original study.

The safety summaries present the relationship of TEAEs to study drug as unrelated or related. In the Phase 2 cIAI and cUTI studies, any TEAE recorded on the CRF as "certain" or "probable" was considered related. Any AE recorded as "not likely" or "unrelated" was considered unrelated. If a subject reported multiple occurrences of the same TEAE, the occurrence assessed by the Investigator as the most related to study drug exposure was used for the analysis.

If the Investigator detected an SAE in a study subject after the end of the period of observation, and considered the event possibly related to prior study treatment, he or she contacted the Sponsor to determine how the AE should be documented and reported. SAEs included any AE at any dose of study drug that resulted in any of the following outcomes:

- Resulted in death
- Was life-threatening (subject was at immediate risk of death at the time of the event; not including an event that hypothetically might have caused death if it were more severe)
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability or incapacity ("persistent or significant disability or incapacity" meant that there was a substantial disruption of a person's ability to carry out normal life functions)
- Was a congenital anomaly or birth defect

- Was an important medical event (important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above were to be considered serious). Examples of such events included:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home
    - Blood dyscrasias
    - Convulsions that did not result in inpatient hospitalization
    - Development of drug dependency or drug abuse

In cases in which a "significant overdose" of the investigational product was taken and a nonserious AE or no AE occurred were to be reported to the Sponsor in an expedited manner. A significant overdose was defined as more than twice the prescribed dose of the investigational product in a single 24-hour period.

In addition, any pregnancy diagnosed in a female subject or in the female partner of a male subject during treatment with the investigational product was to be reported to the Sponsor. Information related to the pregnancy was collected.

ADRs were identified as important adverse reactions experienced by subjects receiving CAZ-AVI, ceftazidime, or avibactam alone while avoiding inclusion of events that would commonly be observed in the absence of CAZ-AVI, ceftazidime, or avibactam administration or would not plausibly be related to CAZ-AVI, ceftazidime, or avibactam.

Adverse events of special interest were identified for five topics: liver disorders, diarrhea, hypersensitivity, hematologic disorders, and renal disorders. Any TEAEs, TEAEs with outcomes of death, SAEs, and TEAEs resulting in discontinuation from study drug or study, as well as laboratory abnormalities representing possible AEs of interest were reviewed across all clinical studies. Potentially clinically significant (PCS) laboratory values relevant to the topics of special interest as well as other relevant abnormal laboratory findings (e.g., AST and ALT > 3×, 5×, and 10× the ULN, or results meeting potential Hy's Law criteria were reviewed.

Other significant adverse events were defined as AEs or laboratory abnormalities deemed by the Sponsor to be of particular clinical importance that were not reported as deaths, SAEs, or discontinuations due to TEAEs. In accordance with regulatory guidance ICH E3 (FDA, 1996), OAEs were identified through medical review of the AEs and laboratory abnormalities for each study and are summarized for each clinical study in the respective CSR. Safety narratives were provided for all deaths, SAEs, discontinuations due to TEAEs, and OAEs.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

As previously mentioned, pooling of data across studies for safety comparisons was not done due to differences in dosages used, patient populations and diseases being studied. Safety

results from individual Phase 1 studies are presented separately in section 5.3. The two Phase 2 trials and open-label Phase 3 trial also differed by indication, study design and dosing regimens. Subjects in the Phase 2 cIAI study received the proposed dose for labeling (although with a shorter infusion time) of CAZ-AVI; the dose of CAZ-AVI was 2.5 g (2 g ceftazidime + 0.5 g avibactam), administered IV over 30 minutes, along with metronidazole 0.5 g IV q8h for 5 to 14 days. In contrast, subjects in the Phase 2 cUTI study received CAZ-AVI 0.625 g (0.5 g ceftazidime + 0.125 g avibactam) IV over 30 minutes q8h for 7 to 14 days, with an oral switch to ciprofloxacin allowed after a minimum of 4 days of IV therapy.

The incidence of adverse events of special interest (i.e., of less frequent but serious reactions such as hepatic dysfunction, nephrotoxicity or skin/allergic reactions), however, were assessed based on the cumulative experience with avibactam or CAZ-AVI during the clinical development program.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the combined Phase 1 and Phase 2 program, 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). The median duration of CAZ-AVI therapy was 5 days.

In the Phase 1 development program, 163 healthy volunteers received avibactam alone, including 14 who received 0.5 g of avibactam alone for 4.5 days or longer and 41 in special patient populations (e.g. renal impairment). Twenty-eight volunteers received CAZ-AVI in combination with metronidazole (MTZ). The majority received 1 to 4 days of study drug. No subject received greater than 11 days. Thirty-six subjects received CAZ-AVI or avibactam alone in multiple dose regimens for 5 to 7 days and 24 subjects received 11 days. Thirty-one subjects received CAZ-AVI at the proposed dose (2.5 g) and approximate duration (4.5 - 10 days).

In the Phase 2 cUTI trial (NXL104/2001), a total of 68 subjects received CAZ-AVI (500/125mg). Most subjects received 4 to 14 days of treatment including CAZ-AVI (intravenous) plus oral switch. Forty-five subjects received 7-14 days of CAZ-AVI. Overall, 14.8% of subjects enrolled were in US sites.

In the Phase 2 cIAI trial (NXL104/2002), a total of 101 subjects received CAZ-AVI + MTZ (2000/500mg). Ninety-six subjects received 5-14 days. Most received 5 to 10 days, median was 6.0 days. Approximately 9% received 11 to 14 calendar days. No subject received > 14 days of study therapy. Overall, 9.4% of subjects enrolled were in US sites.

Table 78: Enrollment by Country and Treatment Group, Phase 2 Studies—Safety Populations

Region	cUTI NXL104/2001			cIAI NXL104/2002		
	CAZ-AVI (N = 68) n (%)	IMI-CS (N = 67) n (%)	Total (N = 135) n (%)	CAZ-AVI + MTZ (N = 101)	MER (N = 102) n (%)	Total (N = 203) n (%)
United States	11 (16.2)	9 (13.4)	20 (14.8)	12 (11.9)	7 (6.9)	19 (9.4)
Bulgaria	—	—	—	6 (5.9)	10 (9.8)	16 (7.9)
France	—	—	—	3 (3.0)	0 (0.0)	3 (1.5)
Poland	—	—	—	1 (1.0)	0 (0.0)	1 (0.5)
Romania	—	—	—	23 (22.8)	34 (33.3)	57 (28.1)
Russian Federation	—	—	—	9 (8.9)	14 (13.7)	23 (11.3)
India	7 (10.3)	5 (7.5)	12 (8.9)	44 (43.6)	36 (35.3)	80 (39.4)
Lebanon	22 (32.4)	25 (37.3)	47 (34.8)	3 (3.0)	1 (1.0)	4 (2.0)
Guatemala	16 (23.5)	17 (25.4)	33 (24.4)	—	—	—
Jordan	12 (17.6)	11 (16.4)	23 (17.0)	—	—	—

Source: Table 1.2.4–1, Sponsor's ISS.

In the on-going Resistant Pathogen Study (D4280C00006) 113 subjects have received CAZ-AVI ± MTZ.

7.2.2 Explorations for Dose Response

In repeat dose toxicity studies in the rat, renal toxicity was observed at very high doses of ceftazidime (> 8 g/kg/day). Avibactam had no significant effects on urinary volume, urinary pH and potassium, and creatinine excretion in rats; however, there was a dose-dependent increase in sodium excretion relative to controls that was statistically significant at 1 g/kg.

Based on clinical experience, no particular dose dependency trends were observed. Table 79 provides the study treatment dosing used in the completed Clinical Pharmacology studies, by treatment group. Single and multiple dose regimens are annotated.

Medical Officer comment: Seizures and neurotoxicity (e.g., myoclonus, NCSE) have been previously described in patients receiving ceftazidime and other β-lactam drugs, particularly in the setting of nephrotoxicity. The pathophysiology may be driven by at least two factors: reduced seizure threshold (more frequent in uremic patients) and increased penetration across the blood-brain barrier with accumulation in the cerebrospinal fluid. As informed by prior experience with ceftazidime and other β-lactams, prescribers have been alerted to the need for cautious dosage adjustment for patients with renal insufficiency. During the CAZ-AVI clinical program, however, no seizures or related neurologic AEs (e.g. myoclonus) were reported. Although formal dose response relationship was conducted, symptoms such as confusion, altered consciousness, dysarthria or myoclonus may indicate the need for EEG evaluation, intensified dialysis and/or dose reduction. These reactions may be more likely to occur, however, in patients who receive the maximum total daily dose of 6 grams/day, or fail to receive proper dose adjustment in the setting of renal impairment.

Table 79: Study Treatment Dosing Used in Phase 1 Clinical Pharmacology Studies

Study Number	Study Treatment and Doses (mg)						
	CAZ-AVI	CAZ Alone	AVI Alone	MTZ + CAZ-AVI	CXL	MOX	MTZ
NXL104/1001	1000 + 250, 2000 + 500 S		50, 100, 250, 500, 1000, 1500, 2000 S				
NXL104/1002	2000 + 500 M		500 S; 500, 750, 1000 M				
NXL104/1003			100 S				
NXL104/1004			500 S				
D4280C00007	3000 + 2000 S				1500 + 2000 S	400 S	
D4280C00008			500 S				
D4280C00009	2000 + 500, 3000 + 1000 M						
D4280C00010	2000 + 500 M		500 M				
D4280C00011	2000 + 500 M	2000 M	500 M				
D4280C00012	2000 + 500 M			500 + 2000 + 500 M			500 M
CXL-PK-01			600 S				

Source: Table 1.2.1–2, Sponsor's ISS. M = multiple dose; MOX = Moxifloxacin; MTZ = metronidazole; S = single dose

The highest dose of avibactam alone, received by 8 subjects (Study NXL104/1001) was 2 g as a single dose infusion. The highest multiple dose infusion of avibactam, received by 8 subjects, was 1 g q8h for 5 days (Study NXL104/1002). The majority of subjects receiving avibactam alone were administered 0.5 g either as single or multiple dose infusions.

The highest dose of CAZ-AVI, received by 46 subjects (Study D4280C00007) was 5 g (3 g ceftazidime + 2 g avibactam) as a single dose infusion. The highest CAZ-AVI dose received in multiple dose regimens was 4 g (3 g + 1 g) q8h for 3 days, received by 21 subjects (Study D4280C00009). A majority of subjects in the CAZ-AVI group received multiple doses of CAZ-AVI 2.5 g.

7.2.3 Special Animal and/or In Vitro Testing

The Applicant conducted adequate non-clinical and clinical studies in pharmacology, pharmacokinetics and toxicology. Please refer to Section 4.3 for additional information.

7.2.4 Routine Clinical Testing

The Applicant conducted adequate routine clinical testing in Phase 2 trials. There was consistency in the reporting of adverse events between verbatim and preferred terms.

7.2.5 Metabolic, Clearance, and Interaction Workup

Both ceftazidime and avibactam are eliminated primarily by the kidneys. Metabolism, excretion and interactions are discussed Section 4.4.3 for additional information.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Specific AEs that are associated with the cephalosporin class of drugs, including liver disorders, diarrhea, hypersensitivity, hematologic disorders, and renal disorders were evaluated and summarized by treatment arm. No findings showing trends or safety concerns indicating that CAZ-AVI had no observable effect on these parameters above that of the comparators was observed in Phase 2 studies. For more details refer to Sections 7.4.1 and 7.4.2. Overall, the AE profile was similar to that of ceftazidime and other cephalosporins.

7.3 Major Safety Results

Overall Incidence

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to AEs and deaths for the two Phase 2 trials and pooled Phase 3 trials is summarized in Table 80. Events in the five ongoing Phase 3 CAZ-AVI studies include four that remain treatment blinded. The overall incidence of events in Phase 3 is similar to the rates in the Phase 2 program.

Table 80: Overall Summary of Treatment-Emergent Adverse Events—Safety Population

	Trial 2001 (cUTI)		Trial 2002 (cIAI)		Phase 3
Subjects with	CAZ-AVI (N = 68) n (%)	IMI-CS (N = 67) n (%)	CAZ-AVI + MTZ (N = 101) n (%)	Meropenem (N = 102) n (%)	Overall (N = 2649) n (%)
Any TEAE	46 (67.6)	51 (76.1)	65 (64.4)	59 (57.8)	n/a
Any SAE	6 (8.8)	2 (3.0)	9 (8.9)	11 (10.8)	180 (6.8)
DAE	2 (2.9)	0 (0.0)	6 (5.9)	4 (3.9)	46 (1.7)
TEAE resulting in Death	0	1 (1.5)	3 (3.0)	2 (2.0)	54 (2.0)

Source: 120 Day Safety Update Report. DAE = Discontinuation of study drug due to TEAE. For Phase 3, deaths and SAEs include events during treatment and within 30 days of the last dose of investigational product.

In the open label Resistant Pathogen study (D4280C00006) in subjects with cIAI or cUTI caused by CAZ-NS pathogens, 8 SAEs 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. Three subjects discontinued study drug due to a TEAE (1 in the CAZ-AVI group, 2 in the BAT comparator group). There were no deaths or discontinuations due to TEAEs in the CAZ-AVI group.

7.3.1 Deaths

In the cumulative CAZ-AVI clinical program, 61 deaths have been reported to date, including 7 in the Phase 2 studies (4 CAZ-AVI, 3 comparator) and 54 in the ongoing Phase 3 studies (11 comparator, 16 CAZ-AVI and 27 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 82. Based on preliminary reports provided in the 120-day safety update on 23 Oct 2014, 6 deaths have been reported in the open-label Study D4280C00006 (3 subjects treated with CAZ-AVI and 3 subjects treated with a BAT comparator). These deaths are summarized in Table 83. 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 81: Overview of Deaths Reported during the CAZ-AVI Clinical Program

	CAZ-AVI	Comparator	Total/Blinded
All Phase 1 (completed/ongoing)	—	—	—
Trial 2001 (cUTI)	0	1	1
Trial 2002 (cIAI)	4	2	6
Phase 3 cIAI (D4280C00001/5)*	13	8	22
Phase 3 cUTI (D4280C00002/4)	—	—	0
cIAI and cUTI (D4280C00006)	3	3	6
cIAI in Asia (D4280C00018)	—	—	3 (1.2%)
HABP/VABP (D4281C00001)	—	—	23 (10.6%)
Total Subjects	20	14	61

*deaths in each treatment arm reported in the mMITT population, one additional CAZ-AVI-treated subject who died after LFU due to a myocardial infarction is not included here.

Narratives

Trial 2001, Subject ID 20304 (IMI-CS): This was an 83-year-old white female with pyelonephritis and baseline urine culture that grew *E. coli*. She received IMI-CS for from (b) (6) (b) (6). Past medical history included coronary artery disease, atrial fibrillation, cerebrovascular accident, type II diabetes mellitus, hypertension, hysterectomy, multiple atrial tachycardia and right hip nailing (performed (b) (6) weeks prior to study entry). On (b) (6), findings on hospital admission included a decreased level of consciousness, abdominal pain and pyuria. Repeat urinalysis on (b) (6) showed 15-20 WBCs, numerous RBCs and bacteria +1. The clinical course was complicated by a silent MI diagnosed by elevated cardiac enzymes on (b) (6); the Investigator felt that the silent MI likely preceded hospitalization and therefore was not a SAE and was not related to the study drug. An indwelling urinary catheter placed during admission was removed prior to discharge from the hospital. On (b) (6) the patient was discharged home in stable condition and prescribed amoxicillin with clavulanic acid, to be taken for one week following discharge. The clinical response at TOC was deemed indeterminate because the subject was not evaluated at the TOC or LFU visits and was considered lost to follow up.

On (b) (6), the patient was seen in the hospital emergency department with complaints of a 3-day history of a decrease in level of consciousness and dysuria followed by anuria associated with abdominal pain. On evaluation, the patient was noted to be hypotensive (BP 80 mm/Hg systolic) and to have purulent return on urinary catheter insertion. WBC was elevated, and urinalysis showed pyuria and was positive for leukocyte esterase. The patient was also reported to have experienced AFIb during this hospitalization. The AFIb was deemed not to be a SAE by the investigator as the patient had a pre-study history of atrial arrhythmia and the event did not otherwise meet serious criteria. The patient was admitted to the ICU for treatment of urosepsis. Treatment was initiated with IV imipenem and with improvement the patient was transferred to a regular floor on (b) (6) for further management. The patient was later noted to have developed GI bleeding on (b) (6) following treatment with heparin and enoxaparin. Sigmoidoscopy showed multiple diverticula and a rectal fistula with the urinary catheter balloon visualized in the rectum. The same day, the patient underwent sigmoidectomy and closure of the bladder with creation of colostomy and right-sided ureterostomy and was transferred to the ICU following surgery and later to a regular floor in stable condition. The patient's urinary bladder ruptured again as evidenced by stool being present in the urine. After discussion with the family it was decided that due to the poor prognosis, the patient would receive palliative care only. The patient became critical experiencing respiratory failure and hypotension over the next two days and suffered cardiopulmonary arrest and died on (b) (6) (b) (6) Urosepsis was reported as a fatal SAE.

Medical Officer comment: I agree with the Investigator and Sponsor assessments that this patient's death and related complications (silent MI, AFib) were due to causes unrelated to the study drug. Although the index infection may have been related to comorbidities such as evolving sigmoid diverticula, comprehensive treatment required emergent surgical intervention in addition to antibacterial treatment. Given her prior cardiac history, however, her pre-surgical risk was high.

Trial 2002, Subject ID 23004 (Meropenem): This was an 82-year-old white female with an intra-abdominal abscess, who was treated with meropenem fo (b) (6) days. Past medical history included history chronic bronchitis, hypertension, chronic pyelonephritis, bilateral crural varices, mastectomy due to mammary gland cancer, and anterior rectal resection due to cancer (2006). She was hospitalized on (b) (6) due to clinical signs of intra-abdominal abscess. Surgery revealed an inter-intestinal abscess with adherent small bowel loops. A debridement and abscessotomy with lavage of the abscess cavity were performed. Baseline APACHE II score was 9, and she was randomized and started on meropenem on 3 Oct. Culture of the abscess cavity grew *Enterobacter aerogenes*; blood cultures were negative. On (b) (6) a small bowel leakage occurred, and repeated surgery was performed; culture of lavage fluid grew *E. faecium*. On (b) (6) (b) (6) the subject died due to secondary diffuse peritonitis, which was considered unrelated to study drug. She was considered a clinical failure at TOC. An autopsy confirmed the cause of death as diffuse serofibrinous peritonitis.

Medical Officer comment: I agree with the Investigator and Sponsor assessments that this patient's treatment failure and death were due to progression of disease given the small bowel leakage and need for repeat surgical intervention.

Trial 2002, Subject ID 32001 (CAZ-AVI + MTZ): This was a 54-year-old white male with no prior medical or surgical history presented with abdominal pain and pus leakage via the umbilicus, who received 1 dose of CAZ-AVI. Abdominal CT showed multiple abdominal and pelvic abscesses. Hartmann procedure and peritoneal drainage were performed for sigmoid colon perforation and multiple abdominal abscesses. Culture of pus from the peritoneum grew *E. coli*, *Fusobacterium necrophorum*, *Prevotella melaninogenica*, *Proteus mirabilis* (CAZ MIC of 16 mg/L, CAZ-AVI MIC of ≤0.03 mg/L), *Enterococcus avium*; blood cultures were positive for *S. epidermis*. Baseline APACHE II score was 6 and the patient was randomized and started on CAZ-AVI + MTZ on (b) (6). Post-operatively, on the same day, the patient had difficulty breathing and was moved to the critical care unit and ventilated under pharmacological sedation. On (b) (6) the patient developed septic shock with hypotension, which required dobutamine. The patient also experienced elevated AST (218 U/L, normal range 5-37) and ALT (267 U/L, normal range 5-41) on (b) (6), which were reported as non-serious AEs and considered to be part of the septic shock. Study drug was discontinued after 2 infusions (1 dose), and piperacillin/tazobactam (Tazocin) and fluconazole were initiated. His clinical outcome, therefore, was considered indeterminate due to an inadequate course of therapy. The patient was extubated and moved to the surgical ward on (b) (6). Respiratory failure and septic shock were reported as SAEs that were life-threatening and resulted in prolonged hospitalization; both events were considered unrelated to study drug. Respiratory failure was considered by the Investigator to be a result of the long anesthesia during surgery and was not considered related to the septic shock.

Subsequently on (b) (6) (post-study), sudden respiratory and cardiac arrest occurred. Resuscitation was initiated, but the patient died. An autopsy was not performed. The site confirmed that the respiratory deterioration was not the continuation of the previously reported SAE of respiratory failure.

Medical Officer comment: Of note, this patient's sudden death occurred (b) (6) days after withdrawal from the study and (b) (6) days after enrollment. He only received 1 dose of CAZ-AVI. Although an autopsy was not performed, sudden cardio-respiratory arrest may have been due to MI or pulmonary embolism. I agree with the Investigator's and Sponsor's assessment that the initial elevation in liver enzymes were due to septic shock, and that the relationship of sudden death to CAZ-AVI were unrelated.

Trial 2002, Subject ID 42005 (CAZ-AVI + MTZ): This subject was a 79-year-old white male with acute appendicitis and a periappendiceal abscess who received (b) (6) days of CAZ-AVI. He was initially admitted to an off-site hospital due to acute appendicitis. During the exploratory laparotomy, surgeons observed a mass that appeared as a cecal inflammatory tumor. The patient decided to be moved to the site hospital where he was admitted on (b) (6). At the

screening visit on (b) (6), the patient was reported to have pain in the right iliac fosa. The same day the patient underwent surgery during which he was diagnosed with abscessed periappendiceal plastron. Culture of pus collected from the peritoneum grew *E. coli*; blood cultures were negative. Baseline APACHE II score was 6. The patient was randomized and received CAZ-AVI + MTZ from (b) (6). On (b) (6) the patient was moved to the ICU due to rapid deterioration in his condition. The patient presented with an altered general status with GCS of 6-7, respiratory hypoxemic failure, metabolic acidosis (arterial pH=7.27), leukocytosis (WBC = 19.6 × 10^3/µL with reference ranges 4-8 × 10^3/µL), coagulopathy (INR = 2.90), renal failure (BUN = 98 mg/dL, with reference ranges 15.0 - 43.0 mg/dL; creatinine = 4.7 mg/dl, with reference ranges 0.6 - 1.3 mg/dl), cardio-vascular failure (HR = 120/min). The patient was treated to manage the hydro-electrolytic and acid-base balance. A chest x-ray showed moderate right pleural reaction and right pneumonia for which drainage was performed. No cultures were performed. As the patient's multiorgan failure worsened, he suffered a cardiac arrest and was unresponsive to any resuscitation measures. The patient died on (b) (6) (Study Day (b) (6)). No autopsy was performed.

Medical Officer comment: I agree with the Investigator's and Sponsor's assessment that this death was most likely due to progression of disease, which appeared to be already significantly advanced given the findings of the initial laparotomy.

Trial 2002, Subject ID 63006 (Meropenem): This was a 59-year-old Asian male with no prior medical or surgical history who presented with abdominal pain and underwent open laparotomy with primary closure of ileal perforation for perforative peritonitis on (b) (6). A culture of pus collected from the peritoneum grew *Klebsiella pneumonia* (MIC for meropenem = 2 mg/L); blood cultures showed no growth. Baseline APACHE II score was 12. Following surgery, the patient was randomized and started on meropenem on (b) (6). Of note, propofol was also used as a sedative of (b) (6). On (b) (6), the patient complained of difficulty breathing. A chest X-ray showed nonhomogenous opacity and obliteration of the costophrenic angle in the left lower lobe region. No blood or sputum cultures were performed. Vancomycin 500 mg q 6 hours IV was initiated (Days (b) (6)). On (b) (6), platelets decreased to 33 × 10^9/L (baseline 265 × 10^9/L). On (b) (6), platelets had dropped to 18 × 10^9/L. Decreased platelet count was reported as an SAE. No clinical evidence of coagulopathy was noticed; therefore a platelet transfusion was not given. On (b) (6) he started gasping and was intubated and put on ventilator support. The patient went into sudden cardiorespiratory arrest; CPR was ineffective and the patient died on Study Day (b) (6) No autopsy was performed. Of note, the clinical response at TOC was considered indeterminate.

Medical Officer comment: I agree with the Investigator's and Sponsor's assessment that the pneumonia, decrease in platelet count and cardiorespiratory arrest were unlikely to be unrelated to meropenem. Although no microbiologic cause of the pneumonia was determined, a gram-positive source, such as MRSA, is likely, and vancomycin was started empirically. The subsequent drop in platelets may also have been multifactorial, including a reaction to propofol and progression of disease (i.e. sepsis) related to the pneumonia.

Trial 2002, Subject ID 67001 (CAZ-AVI + MTZ): This was a 40-year-old Asian male with a medical history of diabetes and sepsis who was hospitalized on (b) (6) for acute pancreatitis with intestinal perforation and received (b) (6) days of CAZ-AVI. Prior antibiotics included ciprofloxacin taken between 21 April and (b) (6). On (b) (6), the patient underwent a thorough necrostomy with subtotal cholecystectomy and multiple intra-abdominal drains. Culture of pus collected from the peritoneum grew *E. coli* (CAZ-R, CAZ-AVI MIC at 2 µg/mL; CMY-42, OXA-1, and CTX-M-15 identified). Blood culture on 13 May showed no growth. Baseline APACHE II score was 5. The patient was randomized and started on CAZ-AVI + MTZ on 13 May. On (b) (6), the patient was noted to have high output of duodenal fistula draining, and on (b) (6), the patient developed acute respiratory distress, high grade fever, and circulatory collapse. Chest X-ray on 22 May showed mild bilateral pleural effusion in both lungs. Culture on 23 May showed no growth. Respiratory distress and worsening of sepsis were reported as SAEs and considered life threatening and unrelated to study medication; no action was taken on study medication. The patient was stabilized by (b) (6) and respiratory distress was considered recovered with sequelae. On 27 May, study medication was discontinued per protocol (patient had received 14 days). The patient was started on cefoperazone and sulbactum (Zostum), linezolid, amikacin, and Amphotericin B. On (b) (6), the patient was moved to another hospital due to financial reasons. On (b) (6), the patient died due to sepsis. Sepsis was considered unrelated to study drug, but he was considered a clinical failure at TOC due to ongoing symptoms of cIAI during the study antibiotic period.

Medical Officer comment: I agree with the Investigator's and Sponsor's assessment that this patient's death was most likely due to progression of disease. It is not clear from the narrative provided, however, whether this subject needed further surgical intervention due to increased drainage on (b) (6).

Trial 2002, Subject ID 72003 (CAZ-AVI + MTZ): This was a 55-year-old white male with a perforated gastric ulcer and peritonitis, abdominal aneurysm and occluded left and right femoral arteries at baseline who underwent emergency laparotomy and bilateral femoral embolectomy. Intraoperative culture of peritoneal fluid grew *E. coli*; blood cultures were not performed. The subject was treated with CAZ-AVI + MTZ for 1 day. On Study Day (b) (6), the subject developed lower extremity pain, absence of lower extremity pulses, chest pain, sweating, and a positive troponin test, and ECG changes were suggestive of myocardial ischemia. The subject's ALT (4.81 × ULN) and AST (5.62 × ULN) were also noted to be elevated on Day (b) (6) and were reported as mild non-serious TEAEs and assessed to be unrelated to study drug. The subject died on Study Day (b) (6) due to cardiac arrest.

Medical Officer comment: This patient had several pre-existing and on-going conditions that made him a high peri-operative risk for MI and subsequent cardiac arrest. I agree with the Investigator and Sponsor's assessment that death was not related to CAZ-AVI nor due to underlying primary infection.

Resistant Pathogen Trial, Subject ID E0205002 (BAT): This was a 76 year-old Hispanic female enrolled on (b) (6). The patient's past medical history included severe aortic stenosis, anemia, cardiac tamponade, COPD, CHF, HTN, thrombocytopenia, colonic diverticulosis, and arrhythmia (supraventricular extrasystoles). The patient received (b) (6) days of comparator starting on (b) (6). The last dose of comparator was administered on (b) (6). On (b) (6), the patient underwent surgery to resolve her pericardial effusion. The planned procedure was placement of a pleuro-pericardial window. On (b) (6), she developed a SAE of severe acute respiratory failure which was assessed as related to complications from the surgical procedure. The patient required supplemental oxygen and CPAP treatment. On (b) (6), at (b) (6) respiratory failure worsened with tachypnea and failure to oxygenate. Mechanical ventilation was initiated. Chest X-ray detected a left-sided hemithorax opacity. Laboratory testing revealed arterial pH 7.11, arterial pCO2 100 mmHg and vital signs revealed a respiratory rate of 28 breaths per minute. Oxygen saturation was 89% on an unknown amount of supplemental oxygen. Bronchoscopy was performed and ventilator-associated tracheobronchitis was diagnosed. Antibiotic treatment was started. The patient worsened and subsequently died from the event of acute respiratory failure on (b) (6). It is unknown whether an autopsy was performed.

Medical Officer comment: Although the narrative provided does not fully describe the primary infection for which the patient was enrolled, the pericardial effusion, surgical procedures and subsequent sequelae are plausible factors leading to cardio-respiratory arrest.

Resistant Pathogen Trial, Subject ID E1801002 (CAZ-AVI): This was an 85 year-old Caucasian female enrolled on (b) (6). The patient's past medical history and concurrent diseases are listed above and included cardiomyopathy, pulmonary tuberculosis, recurrent urinary tract infections, cachexia, anemia, renal insufficiency, dementia, and sleep apnea. The patient received (b) (6) days of CAZ-AVI starting on (b) (6). The last dose of CAZ-AVI was administered on (b) (6). The patient experienced a serious adverse event of severe cardiorespiratory arrest which resulted in death and premature discontinuation of CAZ-AVI. It is unknown if an autopsy was performed.

Medical Officer comment: Although the nature of the primary infection was not fully described in the narrative provided, this patient had multiple risk factors (e.g. cardiomyopathy and advanced age) for MI and subsequent cardiac arrest. Relationship to CAZ-AVI can't be ruled out (e.g. arrhythmia) given the temporal association.

Resistant Pathogen Trial, Subject ID E1803001 (CAZ-AVI): This was an 85 year-old Caucasian female enrolled on (b) (6). The patient's medical history included left hip fracture with arthroplasty, UTI. The patient received (b) (6) days of CAZ-AVI from (b) (6) until (b) (6). The patient experienced an SAE of severe pulmonary embolism on (b) (6) and died on the same day. No treatment was given for this event. It is unknown if an autopsy was performed. The event occurred in the Post Treatment period of this study.

Medical Officer comment: Although the nature of the primary infection was not fully described in the narrative provided. Having had a left hip fracture and arthroplasty, this patient is at a higher risk for thromboembolic complications. It cannot be ruled out, however, that CAZ-AVI may have contributed, since this narrative did not describe when the procedure was done relative to the time of enrollment.

Resistant Pathogen Trial, Subject ID E4002001 (Meropenem): This was a 66 year-old Caucasian, male who was enrolled on (b) (6). The subject's medical history included lung transplantation for emphysema, diverticulosis of colon (without hemorrhage), lower gastrointestinal bleeding, perforation of small bowel, and an ileal conduit. Additional medical history included metastatic transitional cell carcinoma of bladder, iron deficiency anemia, abnormal loss of weight, and rapid AFib. Concomitant medications included enoxaparin sodium, atorvastatin, metronidazole, prednisone, tacrolimus, and vancomycin. Study drug therapy with meropenem was started on (b) (6) for a diagnosis of cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall. The patient experienced a SAE of severe left lower lobe pneumonia and a non-serious AE of metabolic acidosis on (b) (6). The patient was treated with oxygen by mask, BIPAP, IV vancomycin, and IV bicarbonate therapy. The patient refused endotracheal intubation and CPR. Meropenem was discontinued due to the SAE of lobar pneumonia on (b) (6) and the patient died on the same day. The cause of death was respiratory failure due to pneumonia.

Medical Officer comment: I agree with the Investigator and Sponsor that the SAE was not likely related to the study drug. Following lung transplantation, this patient would have been at risk for pneumonia caused by atypical organisms for which the study drug would not have necessarily covered. Given the patient's wish to decline further intervention, death was likely related to progression of pneumonia and unrelated to meropenem.

Resistant Pathogen Trial, Subject ID E4002002 (Meropenem): This was a 78 year-old female subject. The patient's medical history included a cerebral vascular accident, normal pressure hydrocephalus with shunt, chronic renal failure, dementia, HTN, osteoporosis, and hypothyroidism. Concomitant medications included bisoprolol fumarate, levothyroxine sodium, paracetamol, doxazosin mesilate, famotidine, and lamotrigine. Meropenem was started on (b) (6) (b) (6) for Escherichia infection that started on (b) (6). The last dose of study drug was on (b) (6). The patient recovered and was discharged from the hospital to a nursing home for further treatment. The patient experienced an SAE of cardio-respiratory arrest on (b) (6) at the nursing home and died on the same day. The event occurred during the Post Treatment period of the study.

Medical Officer comment: I agree with the Investigator's and Sponsor's assessment that cause of death was likely related to underlying comorbities, including stroke, NPH+shunt, and chronic renal failure.

Resistant Pathogen Trial, Subject ID E7002002 (CAZ-AVI): This is an 85 year-old Hispanic female enrolled on (b) (6). The patient's past medical history and concurrent diseases are listed above and included chronic renal failure, chronic heart failure, diabetes, and anemia. The patient's concomitant medications are listed above and included furosemide and insulin. The patient received (b) (6) days of CAZ-AVI starting on (b) (6). The last dose of CAZ-AVI was administered on (b) (6). During the Post Treatment period of the study, the patient was hospitalized on (b) (6) due to severe worsening of renal failure and anemia, hyponatremia, congestive heart failure and hyperkalemia. The renal failure worsening was thought to be possibly due to low intake of fluids along with diuretic and anti-hypertensive treatment. On (b) (6) (b) (6) lab data showed a serum creatinine of 5.6 and potassium of 6.6. The patient's worsening renal impairment appeared approximately 1 week after completion of CAZ-AVI. The patient received a blood transfusion and fluids. After several days of medical treatment the patient's condition wasn't improving. As per patient's and family's request, palliative care was chosen. The patient died from the event of worsening of renal failure on (b) (6). It is unknown if an autopsy was performed. The causes of death were reported by the Investigator as worsening of renal failure and congestive heart failure.

Medical Officer comment: This patient's cause of death was likely due to underlying comorbidities. It cannot be ruled out however, that CAZ-AVI may have contributed, among other factors including furosemide, to her ongoing/worsening renal failure.

Table 82: Summary Deaths Reported during Trial 2002

ID	Treatment	Treatment-Emergent SAEs Reported	Day of AE	Day of Death	Baseline APACHE II Score	Comment
23004	Meropenem	Secondary peritonitis	(b) (6)		9	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 Septic shock Elevated ALT, AST, bilirubin			6	54-year-old male with perforation of the sigmoid colon, multiple abdominal and pelvic abscesses. Discontinued from study by the investigator on Day (b) (6) due to septic shock.
42005	CAZ-AVI + MTZ	Multiple organ failure (renal, resp, neuro, cardiovasc)			8	79-year-old male with acute appendicitis and peri-appendiceal abscess. Deterioration due to pneumonia with pleural effusion.
63006	Meropenem	Hospital-acquired pneumonia Decrease in platelet count			12	59-year-old male with ileal perforation and peritonitis. Sudden cardiorespiratory arrest on Day (b) (6)
67001	CAZ-AVI + MTZ	Worsening of sepsis			5	40-year-old male with acute pancreatitis and intestinal perforation.
72003	CAZ-AVI + MTZ	Cardiac arrest			18	55-year-old male with perforated gastric ulcer and peritonitis, abdominal aneurysm and occluded bilateral femoral arteries, status post embolectomy.

Table 83: Summary of Deaths Reported during Study D4280C00006

ID	Treatment	Treatment-Emergent SAEs Reported	Day of AE	Day of Death	Comment
E0205002	BAT	Acute respiratory failure	(b) (6)		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			85-year-old female with cardiomyopathy, pulmonary tuberculosis, recurrent UTI, renal insufficiency.
E1803001	CAZ-AVI	Cardiorespiratory arrest, pulmonary thromboembolism			85-year-old female with left hip fracture, status post arthroplasty, UTI
E4002001	Meropenem	Respiratory failure due to pneumonia			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			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			85-year-old female with chronic renal and heart failure. Concomitant diuretics, worsening azotemia, hyperkalemia. Family: palliative care.

7.3.2 Nonfatal Serious Adverse Events

Non-fatal SAEs in Trial 2001 and Trial 2002 are shown in Table 84 and Table 85, respectively. No SAE occurred in more than two subjects in either treatment group. SAEs identified as possibly related to CAZ-AVI were acute renal failure, diarrhea, and increase in hepatic enzymes.

Table 84: Trial 2001 - Subjects with Non-Fatal Serious Adverse Events—Safety Population

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
Blood Creatinine Increased	0	0.0	1	1.5	1	0.7
Total Number of SAEs	7	-	2	-	9	-
Number of Subjects	7	10.3	2	3.0	9	6.7

Table 85: Trial 2002 - Subjects with Non-Fatal Serious Adverse Events—Safety Population

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**	**%**
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
Pneumonia	1	1.0	0	1.0	2	1.0
Postoperative Abscess	1	1.0	1	1.0	2	1.0
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
Wound Secretion	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
Total Number of SAEs	9	-	9	-	18	-
Number of Subjects	7	6.9	9	8.8	16	0.8

In the Resistant Pathogen Study there were 8 SAEs 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.

As of a data cut on 25 June 2014 from the Applicant's 120-day safety update, in the ongoing Phase 3 studies there were 228 SAEs reported in 180 (6.8%) subjects. Treatment group assignments in these studies remain blinded.

7.3.3 Dropouts and/or Discontinuations

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 study drug compared to 11 (16.4%) in the comparator group. Two (2.9%) of the discontinuations were associated with non-fatal SAEs (accidental overdose [Subject 20408] and atrial fibrillation [Subject 11304]) in the CAZ-AVI group. There were no TEAEs resulting in discontinuation in the comparator group.

Table 86: Trial 2001 - Discontinuation of Study Drug (during IV Therapy)—Safety Population

Reasons for Discontinuation	**CAZ-AVI (N = 68) n (%)**	**IMI-CS (N = 67) n (%)**
Completed Study Drug	50 (73.5)	56 (83.6)
Prematurely Discontinued Study Drug	18 (26.5)	11 (16.4)
Due to SAE	1 (1.5)	0
Investigator decision	0	1 (1.5)
Protocol deviation	1 (1.5)	1 (1.5)
Lost to follow up	1 (1.5)	0
Screen failure	12 (17.6)	9 (13.4)
Withdrawal by subject	2 (2.9)	0
Other	1 (1.5)	0

Source: Table 1.2.5.2–2 Sponsor's ISS. Note: for Subject 20408, "protocol violation" was recorded as the reason for discontinuation, but "accidental overdose" was also reported as an SAE as well.

In Trial 2002, 8 subjects (7.9%) in the CAZ-AVI group prematurely discontinued the study compared to 7 (6.9%) in the meropenem group. Two AEs in one subject (pruritic rash and

increase in hepatic enzymes, which was reported as an SAE, 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 6 (5.9%) subjects had TEAEs resulting in discontinuation of study drug in the CAZ-AVI + MTZ group, and 4 (3.9%) in the meropenem group.

Table 87: Trial 2002 - Discontinuation of Study Drug (during IV Therapy)—Safety Population

Reasons for Discontinuation	**CAZ-AVI + MTZ (N = 101) n (%)**	**Meropenem (N = 102) n (%)**
Completed Therapy	93 (92.1)	95 (93.1)
Prematurely Discontinued Study Drug	8 (7.9)	7 (6.9)
Due to AE	4 (4.0)	1 (1.0)
Due to SAE	2 (2.0)	3 (2.9)
Investigator decision	1 (1.0)	0
Protocol deviation	1 (1.0)	0
Lost to follow up	0	2 (2.0)
Other	0	1 (1.0)

Source: Table 1.2.5.2–1 Sponsor's ISS.

In the Resistant Pathogen Study (D4280C00006), 3 subjects discontinued study drug due to a TEAE (1 in the CAZ-AVI group, 2 in the BAT comparator group). 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 (likely unrelated to the study drug). For the two subjects in the BAT comparator group, one subject had lobar pneumonia (unrelated) and the other had CDAD (likely related).

As of 25 June 2014 in the ongoing blinded Phase 3 studies 46 subjects (1.7%) discontinued study drug due to an AE. 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.

7.3.4 Significant Adverse Events

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.

7.3.5 Submission Specific Primary Safety Concerns

Refer to Section 7.7.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The list of Adverse Drug Reactions (ADRs) was determined through review of the TEAEs for possible causal relationship with CAZ-AVI. A subset of TEAEs, were summarized to identify important adverse reactions experienced by subjects receiving CAZ-AVI, ceftazidime, or avibactam alone while avoiding inclusion of events that would commonly be observed in the absence of CAZ-AVI, ceftazidime, or avibactam administration or would not plausibly be related to CAZ-AVI, ceftazidime, or avibactam.

Preferred terms included in the CAZ-AVI ADR list were identified the ceftazidime label and the CAZ-AVI safety database from Phase 1 and Phase 2. Preferred terms were identified if they occurred > 3% in the pooled Phase 1 studies, demonstrated a potential dose response, demonstrated a difference in incidence between groups (CAZ-AVI > comparator), or if they occurred with an incidence > 10% in either Phase 2 trial irrespective of the incidence in the comparator group.

In the Phase 1 studies, the most frequent AEs among subjects receiving avibactam alone were headache (3.4%), diarrhea (2.0%), and application site bruise (2.0%). In the CAZ-AVI only groups, the most frequent AEs were headache (7.9%) and abnormal urine odor (5.2%).

Table 88 and Table 89 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 88: 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 89: 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	9	8.9	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 90: 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 91: 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

Medical Officer comment: The most common TEAEs associated with CAZ-AVI in the treatment of cUTI (from Trial 2001), where incidence was greater in the CAZ-AVI group than comparator (and likely attributable to the drug) were constipation, anxiety and abdominal pain. Headache was the most common TEAE (20.6%), but was reported more frequently in the IMI-CS group (31.3%). For the treatment of cIAI, based on experience from Trial 2002, the most common TEAEs where incidence was greater in the CAZ-AVI +MTZ group than the meropenem group, and can be considered ADRs for the purposed of labeling, were vomiting, nausea and anxiety.

7.4.2 Laboratory Findings

Transient elevations in one or more of the hepatic enzymes, including AST, ALT 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× ULN for AST or ALT plus >2 × ULN for total bilirubin 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. Hy's Law's plots were generated for each trial (Figure 7 for Trial 2001 and Figure 8 for Trial 2002). Although two subjects (Subject ID 11004 and 68020) met the laboratory criteria, upon further review, these max values represented results from screening visits and transaminases subsequently lowered by Day 4 (Table 92).

Figure 7: Hy's Law Plot – Max Bilirubin by ALT and AST (ALP < 2× ULN)—Trial 2001

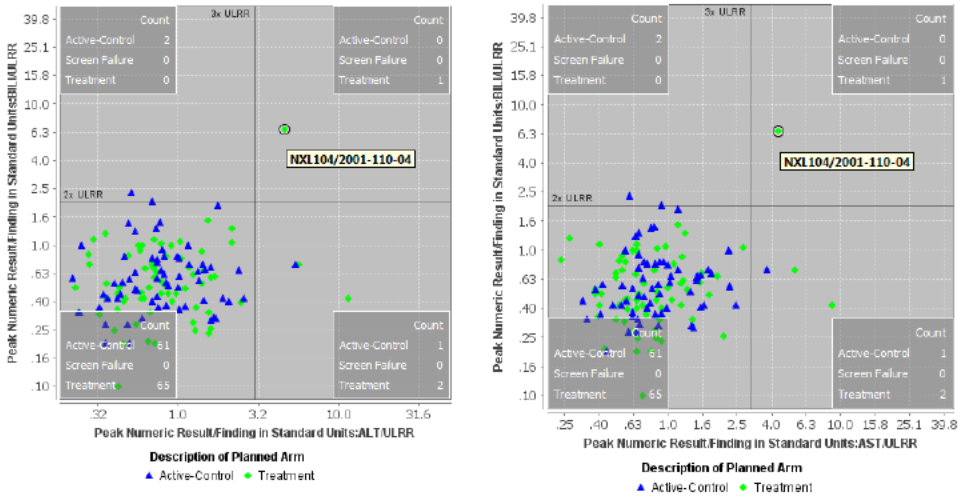


Figure 8: Hy's Law Plot – Max Bilirubin by ALT and AST (ALP < 2× ULN)—Trial 2002

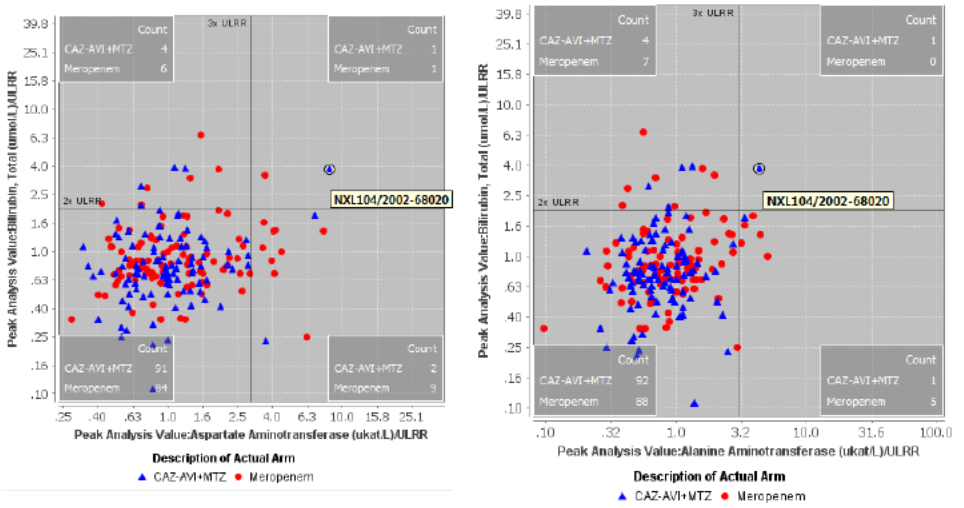


Table 92: Liver Function Tests for Subject 11004 (Trial 2001) and Subject 68020 (Trial 2002)

Patient ID	Age/Sex/ Race	Visit	Study Day	ALT (U/L)	ALT (×ULN)	AST (U/L)	AST (×ULN)	Total Bili (umol/L)	Total Bili (×ULN)	ALP (U/L)	ALP (×ULN)
11004	77/M/White	Screen	-1	303	4.59	195	4.33	135.1	6.58	125	0.99
		EOIV	4	96	1.45	47	1.04	148.8	7.25	265	2.10
68020	35/M/Asian	Screen	-1	173	4.33	339	8.48	64.81	3.79	78	0.27
			4	20	0 5	21	0.53	12.31	0.72	65	0.22

Post-baseline creatinine elevations in the Phase 2 studies were similar to the compactors and ceftazidime alone. Other AEs 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.

A positive Coombs' test is known to occur with administration of β-lactams, with incidences as high as 16% for cefepime. In the Phase 2 studies, the incidence of a positive Coombs' test was <10% for both the CAZ-AVI and comparator groups; 7.3% vs 2.4%, respectively in cIAI and 1.9%

vs 8.3%, respectively in cUTI. None of these subjects had laboratory evidence of hemolysis or other TEAEs representing hematologic disorders.

7.4.3 Vital Signs

Descriptive statistics for the vital sign results at baseline, EOT, TOC, and highest and lowest post-baseline values for the Phase 2 studies presented by treatment arm were reviewed.

Overall, there were no clinically meaningful changes in vital signs associated with CAZ-AVI in either Trial 2001 or Trial 2002. The mean changes in heart rate, respiratory rate, temperature, and systolic and diastolic blood pressure from baseline were small and similar between the CAZ-AVI and comparator treatment arms. The mean decrease observed in heart rate and temperature during therapy in both treatment arms was consistent with subjects improving during the treatment of infection. There were no clinically meaningful differences between the CAZ-AVI and comparator treatment arms for clinically significant physical examination findings at the EOT or TOC visits.

7.4.4 Electrocardiograms (ECGs)

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 EOIV 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 93. For details regarding the Phase 1 QT study, please refer to Section 5.3.5.

Table 93: Summary of QTcF in the Phase 2 Studies—Safety Population

	Trial 2001		**Trial 2002**	
QTcF ECG Parameter	**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

7.4.5 Special Safety Studies/Clinical Trials

Special safety studies, specifically a review of QT analysis, have been discussed previously in Sections 5.3.5 and 7.4.4. No further studies were conducted to specifically assess safety concerns common to other BL/BLI or to demonstrate a safety advantage over alternative antibacterial drugs.

7.4.6 Immunogenicity

CAZ-AVI is not a protein or peptide product; therefore, studies specifically assessing the impact of immunogenicity have not been conducted.

7.5 Other Safety Explorations

Using the MedDRA at a Glance Comparison Analysis tool, adverse events by preferred term were ranked and potential signals were identified for an initial overview and hypothesis generation using risk comparisons between the two treatment arms in the two Phase 2 trials, Trials 2001 and 2002. An adverse event was searched preferred term corresponding to the body system or organ class (AEBODSYS) and dictionary-defined term (AEDECOD) from the adverse event (AE) dataset. Only adverse events starting between subjects' first exposure and 30 days after subjects' last exposure were included in the analysis. Each adverse event was counted only once per subject. Treatment arm was determined using the planned treatment arm (ARM) from DM. From Trial 2001, TEAE's with potential signals identified were GI disorders (constipation and upper abdominal pain), fungal urine infection, diabetes mellitus, and dizziness. From Trial 2002, potential signal identified were leukocytosis, vomiting, asthenia, pain, UTI, wound complication, incision site pain, increased eosinophil count, anxiety, hypokalemia, and respiratory distress.

7.5.1 Dose Dependency for Adverse Events

Because Trial 2001 (cUTI) used a dose that was 25% of that used in Trial 2002 (cIAI), the Applicant conducted a search for ADRs in an exploration for potential dose response. The preferred terms identified in the Phase 2 studies were inferred by identifying any term with a difference > 5% in incidence between groups (subjects in the CAZ-AVI + MTZ group in the Trial 2001 minus subjects in the CAZ-AVI group in Trial 2001). The incidence in the IV-only treatment period of the cUTI trial was used. Nausea and vomiting were the only two adverse reactions identified. Of note, however, the terms ALT increased, AST increased, blood ALP increased, and pyrexia from the Phase 2 cIAI study were not included as these terms were likely related to the underlying intra-abdominal infection.

7.5.2 Time Dependency for Adverse Events

Since CAZ-AVI was studied for acute treatment (no longer than 14 days), there are limited data available to explore time dependence of adverse events with prolonged use.

7.5.3 Drug-Demographic Interactions

Based on Phase 1 experience, incidences of TEAEs were higher among the subjects who received avibactam alone in the special populations group (36.6% [15]) who were ≥ 65 years old or had moderate to severe renal impairment compared to subjects who received avibactam alone in the healthy volunteers population (16.6% [27]) who were < 65 years old and had normal renal function or mild renal impairment.

Incidences of AEs in the Phase 2 trials were reviewed based on based on gender, race, ethnicity or region. No significant differences in safety were found; however, assessments were limited due to the small numbers of subjects within each subgroup.

Table 94: Trial 2001 – Adverse Event Rate by Demographic Subgroup—Safety Population

Demographic Subgroup	CAZ-AVI (N= 68) n/N (%)	IMI-CS (N= 67) n/N (%)
Overall	47/68 (69.1)	52/67 (77.6)
Gender		
Male	10/17 (58.8)	14/18 (77.8)
Female	37/51 (72.5)	38/49 (77.6)
Age Category		
18 to 64	41/57 (71.9)	42/55 (76.4)
≥65	6/11 (54.5)	10/12 (83.3)
≥75	3/6 (50.0)	9/10 (90.0)
Race		
White or Caucasian	28/40 (70.0)	32/41 (78.0)
Black/African American	1/2 (50.0)	4/5 (80.0)
Asian	4/8 (50.0)	3/5 (60.0)
Other	14/18 (77.8)	13/16 (81.3)
Ethnicity		
Hispanic or Latino	14/18 (77.8)	15/18 (83.3)
Not Hispanic or Latino	33/50 (66.0)	37/49 (75.0)
Region		
US	8/11 (72.7)	9/9 (100.0)
Rest of World	37/57 (64.9)	43/58 (74.1)

Table 95: Trial 2002 – Adverse Event Rate by Demographic Subgroup—Safety Population

Demographic Subgroup	CAZ-AVI + MTZ (N = 101) n/N (%)	Meropenem (N = 102) n/N (%)
Overall	61/101 (60.4)	59/102 (57.8)
Gender		
Male	42/70 (60.0)	46/81 (56.8)
Female	19/31 (61.3)	13/21 (61.9)
Age Category		
18 to 64	56/94 (59.6)	50/88 (56.8)
≥65	5/7 (71.4)	9/14 (64.3)
≥75	1/2 (50.0)	3/3 (100.0)
Race		
White or Caucasian	34/56 (60.7)	36/65 (55.4)
Black/African American	0/0	1/1 (100.0)
Asian	15/32 (46.9)	9/23 (39.1)
American Indian or Alaskan Native	1/1 (100.0)	0/0
Other	11/12 (91.7)	13/13 (100.0)
Ethnicity		
Hispanic or Latino	2/3 (66.7)	1/2 (50.0)
Non-Hispanic or Latino	59/98 (60.2)	58/100 (58.0)
Region		
US	10/12 (83.3)	7/7 (100.0)
Rest of World	51/89 (57.3)	52/95 (54.7)

7.5.4 Drug-Disease Interactions

Refer to Section 7.7.

7.5.5 Drug-Drug Interactions

Please refer to Dr. Seong Jang's review of clinical pharmacology.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The proposed recommended duration of CAZ-AVI treatment is at most 14 days. There have been no formal studies in humans to assess the carcinogenic effects.

7.6.2 Human Reproduction and Pregnancy Data

Ceftazidime is designated Pregnancy Category B. Reproduction studies of ceftazidime performed in mice and rats at doses up to 40 times the human dose have revealed no evidence of impaired fertility or harm to the fetus due to ceftazidime.[5] There are, however, no adequate and well-controlled studies of ceftazidime in pregnant women.

Reproductive and developmental toxicology studies of CAZ-AVI have not been performed; however, such studies with avibactam during early pregnancy in rats and rabbits at doses that resulted in exposure to avibactam of 9 and 2 times, respectively, the exposure in humans have been performed. Please also refer to the Animal Pharmacology/Toxicology review by Armand Balboni, JD, PhD and Wendelyn Schmidt, PhD for further details.

There have been 3 reports of pregnancy and exposure to blinded study drug during the ongoing Phase 3 studies (Subjects D4280C00004-E6205008, D4280C00005-E1902001, and D4280C00005-E7803007). One subject experienced a normal delivery, one subject had an elective abortion, and the outcome of the third pregnancy is unknown at this time.

Ceftazidime is excreted in human milk in low concentrations. There are no data for avibactam on dosing adjustments during pregnancy or during lactation. In addition, no studies have been performed with avibactam to determine its presence in human milk; however, avibactam was shown to be excreted in the milk of rats in a dose dependent manner. Because many drugs are excreted in human milk, including ceftazidime, the proposed label recommends that caution should be exercised when CAZ-AVI is administered to a nursing woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

To date, pursuant to PREA requirements, a single-dose PK study (D4280C00014) in subjects from 3 months to less than 18 years of age with a suspected or confirmed bacterial infection and receiving other systemic antibacterial therapy has recently completed, but study reports have not yet been submitted. The Applicant submitted a deferral request with their initial pediatric study plan (iPSP), which assumes that efficacy can be extrapolated from adult data for cIAI and cUTI in pediatric patients as young as 3 months of age. Pending determination of appropriate doses for each age group, a multiple-dose, active-controlled trial will be conducted to evaluate safety, tolerability and efficacy of CAZ-AVI in children with cUTI and cIAI from 3 months to less than 18 years of age. An additional safety and PK study is included for neonates from birth to 3 months as well.

Non-clinical studies of ceftazidime ± avibactam did not indicate any potential effects on growth within the range of clinically relevant doses of CAZ-AVI. (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Ceftazidime and BL-BLI combinations are not known to be associated with withdrawal phenomena; therefore, no potential for abuse or withdrawal would be expected. No additional studies were conducted by the Applicant related to withdrawal phenomena and/or abuse potential.

7.7 Additional Submissions / Safety Issues

In amendments to the NDA, the Applicant submitted preliminary analyses of unblinded data from the completed Phase 3 cIAI trial (from combined protocols D4280C00001/5, also referred to as RECLAIM) on 09 Oct 2014, 16 Oct 2014, 07 Nov 2014 and 21 Nov 2014.

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 < 70 mL/min in Trial 2001 and < 50mL/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 96).

Table 96: 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 97. 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 97: 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.

At the AIDAC on 5 Decemeber 2014, the Applicant stated that they are expecting completion of data analysis and submission of the final clinical study reports for the Phase 3 trials in cIAI and cUTI in late 2015.

Medical Officer comment: 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.

Because the percentage of time that free-drug concentrations are above the minimum inhibitory concentration (%*f*T > MIC) is the most relevant PK/PD index for ceftazidime, and the Fortaz label allows an increase in the total daily ceftazidime dose of 50% (to no more than 6 grams) for severe infections, an increase in frequency to the initially proposed renal dosing adjustments is recommended.

Table 98: Amended Dosing Regimen for CAZ-AVI in Patients with Renal Impairment

Estimated Creatinine Clearance (mL/min)[a]	**Recommended Dosage Regimen for CAZ-AVI**
> (b) (4) to ≤ 50	1.25 g (1.0 g ceftazidime + 0.25 g avibactam) IV (over 2 hours) every 8 hours
> (b) (4) to ≤ 30	0.94 g (0.75 g ceftazidime + (b) (4) g avibactam) IV (over 2 hours) every 12 hours
> (b) (4) to ≤ 15[b]	0.94 g (0.75 g ceftazidime + (b) (4) g avibactam) IV (over 2 hours) every 24 hours
≤ 5[b]	0.94 g (0.75 g ceftazidime + (b) (4) 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, AVYCAZ should be administered after hemodialysis on hemodialysis days.

8 Postmarket Experience

As of the date of this application's submission, CAZ-AVI has not been marketed anywhere in the world.

Ceftazidime has been marketed throughout the world since its approval in 1985. 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.

As recommended by the Division, a review of safety information related to the postmarketing clinical experience of ceftazidime is provided. 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 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.

9 Appendices

9.1 Literature Review/References

The Applicant conducted a meta-analysis to estimate the treatment effect of ceftazidime and determine the extent to which avibactam preserves the clinical activity of ceftazidime. Most of the studies cited, however, were open label and used analysis populations that may not reflect the patient population studied in the CAZ-AVI clinical trial population. Please refer to Dr. Gamalo's statistical review of sponsor's meta-analysis for the estimate of historical effect of ceftazidime in cIAI and cUTI.

A list of references cited throughout this review is also provided at the end of this document on page 156.

9.2 Labeling Recommendations

Throughout

- Placeholder "TRADENAME" replaced by "AVYCAZ".
- "Antibiotic", "antimicrobial" and "antimicrobial agent" replaced by "antimicrobial drug" for consistency.
- Abbreviations and symbols (e.g. >, <, IV, and g) replaced by full terms.
- Dose of AVYCAZ referred to as both combined and by component [e.g. 2.0 grams ceftazidime/0.5 grams avibactam).

Highlights

- Edited for brevity (sections should take up no more than ½ page). Table with dosing instructions consolidated with renal dosing.
- Statement regarding development of drug-resistance moved to Indications and Usage subsection in keeping with Division's convention.
- (b) (4).

Section 1: Indications and Usage

- For each indication (cIAI and cUTI), the following statement added: "As only limited clinical safety and efficacy data for AVYCAZ are currently available, reserve AVYCAZ for use when limited or no alternative treatment options are available."
- (b) (4)
- Species who were identified for cUTI and cIAI in the Fortaz label maintained.
- New organisms studied in Phase 2 trials with CAZ-AVI were not included (e.g. *Pseudomonas stutzeri*) since an adequate subset of patients with this organism were not identified.
- Statement in parentheses following *Escherichia coli*, (b) (4), was omitted for cIAI and cUTI. (There were only 2 subjects in the cIAI trial

and only 2 of 3 subjects in the cUTI trial who were identified and had favorable outcomes).

Section 4: Contraindications

- Sentence describing [redacted] (b) (4) " was omitted (redundant).

Section 5: Warnings and Precautions

- Warning for decreased clinical response in patients with moderate/severe renal impairment (CrCL 50 ml/min or less) at baseline. Patients should have CrCL monitored during therapy daily with dose adjusted accordingly.
- Section 5.4 Central Nervous System Reactions: since NCSE was not just observed in patients with renal impairment, regardless of dose adjustment, "particularly…" was inserted.

Section 6: Adverse Reactions

- Separate sections added for each indication on the basis of different patient populations and use of different doses.
- Important inclusion/exclusion criteria added (i.e. baseline creatinine clearance).
- ADR table relisted to include only reactions that had higher incidence rate than the comparator.
- Heading for "Increased Mortality" added to describe findings from the Phase 3 cIAI trial.
- The reactions listed section "Other Adverse Reactions of TRADENAME and Ceftazidime" were combined, but should be separated for CAZ-AVI and ceftazidime.

Section 11: Description

- Sodium content added.

Section 12: Clinical Pharmacology

- [redacted] (b) (4).
- [redacted] (b) (4)
- Description of animal models abridged.
- [redacted] (b) (4).
- [redacted] (b) (4)

Section 13: Nonclinical toxicology

- [redacted] (b) (4)

Section 14: Clinical Studies

- Statutory labeling requirements allow discussion of results of "adequate and well-controlled trials"; however, the results presented proposed were not substantiated by inferencial testing. Section combined for abridged discussion.
- [redacted] (b) (4).

Please refer to final labeling as attached to the Action Letter.

9.3 Advisory Committee Meeting

The Anti-Infective Drug Advisory Committee (AIDAC) convened for the discussion of NDA-206494 on 5 December 2014.

Questions to the Committee:

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? VOTE

   YES: 11 NO: 1 ABSTAIN: 0

Committee Discussion: *Although the committee generally agreed that CAZ-AVI was likely to fulfill an important area of unmet need, it is important that there continue to be long-term assessment of safety and efficacy, including additional information regarding combination effects with other antibacterial drugs. A REMS-like strategy, a mandatory Phase 4 study in resistant pathogens, therapeutic drug monitoring, and consideration of continuous infusion were also suggested.*

   a. If yes, please provide any recommendations concerning labeling.

Committee Discussion: *The committee members who voted "Yes" noted that it was reassuring to see activity of the CAZ-AVI in subjects with CAZ-NS pathogens. Some preliminary Phase 3 data, although not fully vetted by the FDA, was informative. Most committee members were concerned about the imbalance in mortality and clinical response in subjects with baseline moderate renal impairment. One member stated that this was an important "red flag" and patients requiring dosing adjustments due to renal impairment should be excluded from receiving CAZ-AVI until more data is available for appropriate dosing recommendations. Some committee members, however, felt that this did not rise to the level of requiring a boxed warning. An additional caveat was that in multi-drug resistant infections, particularly for Pseudomonas, CAZ-AVI may not be sufficient as monotherapy.*

   b. If no, what additional studies/analyses are needed?

Committee Discussion: *Dr. Dekker was the only member who voted "NO". His concern was that there is no regulatory mechanism to enforce the limited use labeling. He reiterated concern regarding safety issues from the Phase 3 cIAI trial as previously mentioned.*

2. Has the applicant demonstrated substantial evidence of safety and efficacy of ceftazidime-avibactam for the proposed indication of complicated urinary tract infections, when limited or no alternative treatments are available? VOTE

YES: 9 NO: 3 ABSTAIN: 0

Committee Discussion: *The majority of the committee noted that reasons for their decision were the same as they were for the cIAI indication.*

a. If yes, please provide any recommendations concerning labeling.

Committee Discussion: *Dr. Cappelletti suggested making checking with urinary concentrations of the drug in patients with renal impairment. Also of note, the newly updated breakpoints for ceftazidime are currently predicated on 1 grams q8h. Dr. Reller thought that the higher dose proposed for CAZ-AVI is reassuring, but thought that the CAZ-AVI breakpoints should be same as the current CAZ breakpoints (i.e. for Pseudomonas with a dose of 2 grams q8h, the breakpoint should be 16).*

b. If no, what additional studies/analyses are needed?

Committee Discussion: *Dr. Decker and Ms. McCall both voted "NO" because they were concerned about the high (40%) failure rate in cUTI trial, for which it was unclear how much could be contributed to PK/PD considerations. Dr. Follmann, who also voted "NO", was concerned about insufficient data, since results from the Phase 3 cUTI trial are not yet available, and he did not comfortable recommending approval based on Phase 2 data only.*

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, when limited or no alternative treatments are available? VOTE

YES: 0 NO: 12 ABSTAIN: 0

Committee Discussion: *Prior to the vote, the committee asked for clarification of the requested indication and the question as worded. The Sponsor stated they are proposing this indication "… with no alternative treatments" instead of "… with limited treatment options." The panel was instructed to vote on the question as worded, and Question 4 was added for the same indication "… with no alternative treatments."*

a. If yes, please provide any recommendations concerning labeling.

Committee Discussion: *None of the members voted "YES".*

b. If no, what additional studies/analyses are needed?

Committee Discussion: *All of the committee members cited the lack of human data as the reason for their "NO" vote. They stated that consideration of the HABP/VABP indication should*

be deferred pending the results of the ongoing Phase 3 HABP/VABP trial. Dr. Reller was also concerned that approving it for this indication may encourage inappropriate use. Additionally, HABP/VABP is the most difficult to treat. Approving without clinical data should not be endorsed. Dr. Magill was concerned that approval would limit the collection of additional crucial data.

4. 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, when no alternative treatments are available? VOTE

   YES: 1 NO: 11 ABSTAIN: 0

a. If yes, please provide any recommendations concerning labeling.

Committee Discussion: *Dr. Andrews was the only member who voted "YES". Her change in vote from Question 3 was based on the "… with no alternative treatment" language. She wanted to send a strong message of flexibility to pharmaceutical companies.*

b. If no, what additional studies/analyses are needed?

Committee Discussion: *As with Question 3, lack of human data remained problematic for each of the committee members, as even availability of some data would have been informative. If approved for other indications, however, absence of this indication does not preclude "off-label" use. It is Sponsor's duty to publish the data they have, and it is within the purview of IDSA to make guideline recommendations based on all data available. Some committee members noted that it would be helpful for prescribers to have non-clinical data (whether in the label or in published data), such as lung penetration from ELF studies, to be able to make informed decision about "off-label use". Dr. Reller noted that, unlike cUTI or cIAI, where the infection can be drained by the urine or surgical intervention, lung cannot be routinely debrided. Not approving this indication at this time highlights the need to obtain sufficient data. Duration of treatment recommended is vague and highlights need for a study.*

References

[1] Drawz SM, Bonomo RA. Three decades of beta-lactamase inhibitors. *Clin Microbiol Rev*. 2010;23(1):160-201.
[2] Hoban DJ, et al. Susceptibility of gram-negative pathogens isolated from patients with complicated intra-abdominal infections in the United States, 2007-2008: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrob Agents Chemother*. 2010;54(7):3031-4.
[3] Zerbaxa™ [US Package Insert]. Lexington, MA: Cubist Pharmaceuticals, Inc.; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206829lbl.pdf
[4] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: twenty third informational supplement. Clinical and Laboratory Standards Institute. CLSI M100 S23. Clinical and Laboratory Standards, 2013. Wayne, PA.
[5] Fortaz® [US Package Insert]. Cary, NC: Covis Pharmaceuticals, Inc.; 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050578s055,050634s023lbledt.pdf
[6] Stachyra T, et al. Mechanistic studies of the inactivation of TEM-1 and P99 by NXL104, a novel non-beta-lactam beta-lactamase inhibitor. *Antimicrob Agents Chemother*. 2010; 54(12):5132-8.
[7] Winkler ML, et al. Unexpected challenges in treating multidrug-resistant gram-negative bacteria: resistance to ceftazidime-avibactam in archived isolates of *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother.* 2015; 59:1020-9.
[8] Bonnefoy A, et al. In vitro activity of AVE1330A, an innovative broad-spectrum non-beta-lactam beta-lactamase inhibitor. *J Antimicrob Chemother*. 2004;54(2):410-7.
[9] Capel-Edwards K, Losty CR, Tucker ML, Pratt DA. Pre-clinical safety evaluation of ceftazidime. *J Antimicrob Chemother*. 1981; 8 Suppl B:237-9
[10] FDA Draft Guidance for Industry - Complicated Urinary Tract Infections: Developing Drugs for Treatment. (issued by CDER, February 2012). http://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BENJAMIN D LORENZ
02/12/2015