NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number	206494
Priority or Standard	Priority
Submit Date(s)	9/14/18
Received Date(s)	9/14/18
PDUFA Goal Date	3/14/18
Division/Office	CDER/OND/OAP/DAIP
Review Completion Date	3/11/19
Established Name	Ceftazidime-avibactam
(Proposed) Trade Name	AVYCAZ
Pharmacologic Class	Cephalosporin (beta-lactam) and beta-lactamase inhibitor combination antibacterial drug
Code name	Not Applicable
Applicant	Allergan
Formulation(s)	Injection, supplied as a sterile powder for constitution in single-dose vials
Dosing Regimen	Dosing based on age, weight, and renal function; see review for detail
Applicant Proposed Indication(s)/Population(s)	For the treatment of the following infections caused by designated susceptible Gram-negative microorganisms: • Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole, in pediatric patients 3 months and older • Complicated Urinary Tract Infections (cUTI), including Pyelonephritis, in pediatric patients 3 months and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of the following infections caused by designated susceptible Gram-negative microorganisms: • Complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole, in patients 3 months and older • Complicated Urinary Tract Infections (cUTI), including Pyelonephritis, in patients 3 months and older

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OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Glossary

AC	Advisory committee
AE	Adverse event
AR	Adverse reaction
AUC	Area under the curve (drug concentration versus time)
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CEF	Cefepime
CFR	Code of Federal Regulations
cIAI	Complicated intra-abdominal infection
CMC	Chemistry, manufacturing, and controls
CR	Carbapenem-resistant
CrCl	Creatinine clearance
CRE	Carbapenem-resistant Enterobactericeae
CRF	Case report form
CSR	Clinical study report
cUTI	Complicated urinary tract infection
DAIP	Division of Anti-Infective Products
ECG	Electrocardiogram
ERT	Ertapenem
ESBL	Extended spectrum beta-lactamase
eCTD	Electronic common technical document
FDA	U.S. Food and Drug Administration
GCP	Good clinical practice
GNR	Gram-stain negative rod
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ITT	Intent to treat
IDSA	Infectious Disease Society of America
MDR	Multiple drug resistant
MedDRA	Medical Dictionary for Regulatory Activities
MER	Meropenem
MIC	Minimum inhibitory drug concentration of microbial growth
Micro-ITT	Microbiological intent to treat
mITT	Modified intent to treat
NDA	New drug application
NME	New molecular entity
NOAEL	No observed adverse effect level
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PD	Pharmacodynamics
PI	Prescribing information or package insert
PK	Pharmacokinetics
PMC	Post-marketing commitment
PMR	Post-marketing requirement
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
PT	Preferred term
PTA	Probability of target attainment
q8h	Every 8 hours
QIDP	Qualified infectious disease product
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ classification
SRP	Surgical review panel
TOC	Test of cure
TEAE	Treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Ceftazidime-avibactam (CAZ-AVI; AVYCAZ®) is a fixed combination antibacterial drug product composed of ceftazidime, a third-generation cephalosporin, and avibactam, a non-β-lactam β-lactamase inhibitor at a ratio of 4:1. Ceftazidime was first approved in 1985 (FORTAZ®, NDA 50578) for the treatment of lower respiratory tract infections, skin and skin structure infections, urinary tract infections, intra-abdominal infections, gynecological infections, bacterial septicemia, and central nervous system infections. Ceftazidime is approved for use in pediatric patients, including neonates aged 0 to 4 weeks. Avibactam is a beta-lactamase inhibitor that does not have antibacterial activity at the labeled dose, but rather protects ceftazidime from degradation by a range of bacterial beta-lactamase enzymes (Ambler Class A, Class C, and some Class D β-lactamase enzymes).

AVYCAZ was initially approved in February 2015 for the treatment of adults with complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in patients with limited or no alternative treatment options. Due to the limited clinical data submitted in the original application, the drug was approved with a statement of limited use. Two subsequent efficacy supplements provided clinical trial data in adult patients to support the removal of the limited use statements. The efficacy supplement for cIAI was approved on June 22, 2016 (Supplement 2) and cUTI on January 26, 2017 (Supplement 3). The dosing of AVYCAZ is the same across indications for patients aged 18 or more years, namely 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) every 8 hours by intravenous (IV) infusion over 2 hours. The dose is modified for patients with impaired renal function.

This efficacy supplement proposes to add a new population, treatment of cIAI and cUTI in pediatric patients aged ≥3 months to 18 years. The supplement was submitted in response to the Pediatric Research Equity Act (PREA) post-marketing requirements (PMR) 2862-1 (cUTI) and 2862-2 (cIAI) for AVYCAZ. The Applicant met the dates set for study completion (September, 2017) and sNDA submission (September, 2018). For the purposes of record keeping, the supplement was divided into two efficacy supplement numbers. Efficacy supplement 005 refers to the cUTI indication, and supplement 006 is for cIAI. This review analyzes the indications jointly.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence to support the approval of AVYCAZ for the treatment of cIAI and cUTI in pediatric patients aged ≥3 months to 18 years. Data from two single-blinded, randomized, multicenter active-controlled studies of pediatric patients aged ≥3 months to 18 years were submitted. Study D4280C00015 compared AVYCAZ + metronidazole to meropenem for treatment of cIAI. Study D4280C00016 compared AVYCAZ to cefepime for

treatment of cUTI. The primary endpoint in these trials was to establish safety and tolerability of AVYCAZ in the pediatric patient population, and secondary endpoints evaluated pharmacokinetics (PK) as well as efficacy. Between the two studies, there were 128 pediatric patients exposed to AVYCAZ (Table 1)

Table 1: Summary of the Pediatric Study Population Exposed to AVYCAZ

	Patients exposed to AVYCAZ (N=128)		
Age Cohort	cIAI	cUTI	Total
Cohort 1: 12 to <18 years	22	13	35
Cohort 2: 6 to <12 years	33	17	50
Cohort 3: 2 to <6 years	6	11	17
Cohort 4a: 1 to <2 years	0	12	12
Cohort 4b: 3 months to <1 year	0	14	14
Total	61	67	128

The trials were not designed for inferential testing of AVYCAZ efficacy in the pediatric patient population. The efficacy of AVYCAZ is extrapolated from the adult population for these indications as the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients; therefore, the cIAI and cUTI trial results are presented descriptively to support the use of AVYCAZ in the pediatric population. The pharmacokinetic (PK) results from the clinical trials demonstrate that the AVYCAZ exposure in pediatric patients with cIAI and cUTI at the proposed doses is reasonably similar to the exposure in adult patients receiving the approved dose.

In the cIAI study, the clinical response rate for the intent to treat (ITT) population was 91.8% and microbiological response rate was 90%. There were no relapses, emergent infections or persistent pathogens with increasing MIC. At the test of cure (TOC) visit in the cUTI study, the clinical response rate for the ITT population was 86.8% and the microbiological response rate was 79.6%. There were 4 relapses, 3 of which were in patients with urological abnormalities. There were no persistent pathogens cultured with an increasing minimum inhibitory drug concentration (MIC). Detailed analyses of the trial results are provided in section 7 of this review.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

AVYCAZ (Ceftazidime-avibactam, CAZ-AVI) is approved for the treatment of cIAI, cUTI and hospital-associated bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) in adults. This efficacy supplement proposes to add pediatric patients aged ≥3 months to 18 years to the cIAI and cUTI indications. The dosing regimen for both indications is age and weight-based, administered every 8 hours for 5 days (cIAI) or 7 days (cUTI) to 14 days by intravenous (IV) infusion over 2 hours.

Data from two single-blind, randomized, multicenter active-controlled studies of pediatric patients aged ≥3 months 18 years was submitted to support the use of AVYCAZ in the proposed pediatric population. The two studies enrolled a total of 128 pediatric patients exposed to AVYCAZ with the primary objective of evaluating AVYCAZ safety and tolerability. The efficacy of AVYCAZ was extrapolated from the adult population for these indications; therefore, the cIAI and cUTI trial results were presented descriptively to support the use of AVYCAZ in the pediatric population.

Study D4280C00015 compared AVYCAZ + metronidazole to meropenem for treatment of cIAI. Patients received IV treatment for a minimum of 72 hours before an optional switch to oral therapy at the discretion of the investigator to complete a total of 7 to 15 days of antibacterial therapy. The intent-to treat (ITT) population consisted of 83 patients (AVYCAZ plus metronidazole, n=61, meropenem n=22) who were randomized to receive treatment. At the test of cure (TOC) visit in the cIAI study, which occurred 8 to 15 days after the last dose of study drug, the clinical response rate in the ITT population was 56/61 (91.8%) for AVYCAZ, and 21/22 (95.5%) for meropenem. In the microbiological-ITT (micro-ITT) population, comprised of patients who had a baseline pathogen known to cause cIAI, the favorable response rate was 45/50 (90%) and 18/19 (94.7%) for AVYCAZ and meropenem, respectively. There were no relapses or pathogens that developed an increasing MIC with treatment.

Study D4280C00016 compared AVYCAZ to cefepime for treatment of cUTI. Patients received IV treatment for a minimum of 72 hours before an optional switch to oral therapy at the discretion of the investigator to complete a total of 7 to 14 days of antibacterial therapy. A total of 95 patients with cUTI received study medication (AVYCAZ, n=67, cefepime n=28). At the TOC visit, which occurred 8 to 15 days after the last dose of study drug, the combined clinical and microbiologic response rate in the micro-ITT population was 39/54 (72.2%) for AVYCAZ and 14/23 (60.9%) for cefepime. The clinical and microbiological response rates for AVYCAZ were 48/54 (88.9%) and 43/54 (79.6%), respectively,

compared to the clinical and microbiological response rates for cefepime of 19/23 (82.6%) and 14/23 (60.9%), respectively. Sensitivity analyses that considered clinical response at different time points (i.e., at end of therapy, at study completion) were consistent with the efficacy findings at the TOC. In both studies, there were no pathogens isolated with an increasing AVYCAZ MIC relative to baseline.

The safety profile of AVYCAZ in the pediatric studies was similar to the safety profile of AVYCAZ in adults with cUTI and cIAI. Treatment Emergent Adverse Events (TEAEs) up to the last study visit occurred at a similar rate in subjects who received AVYCAZ (53.1%) as compared to those who received a comparator treatment (56.0%). There were no deaths and no new safety signals identified. Serious adverse events were infrequent, but did lead to discontinuation of AVYCAZ in 3 patients with cUTI. The most common adverse events were diarrhea in the cUTI group and vomiting and infusion site reactions in the cIAI group. There were no concerning trends in laboratory values and no Hy's law cases were reported. The major risks associated with AVYCAZ use include anaphylaxis, *C. difficile* associated diarrhea, and central nervous system reactions (seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia); however, these adverse reactions were not observed in the pediatric studies.

Overall, AVYCAZ has a favorable safety and efficacy profile for the treatment of cIAI and cUTI in pediatric patients aged ≥3 months to 18 years. The risks associated with AVYCAZ use in the pediatric population can be adequately addressed through the product labeling and routine post-marketing surveillance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• cIAIs are serious infections that extend beyond the hollow viscus of origin into the peritoneal space and are associated with either abscess formation or peritonitis and systemic signs and symptoms of illness. Etiology of cIAI in pediatric patients depends on age group and comorbidities, and is usually treated with a combination of antibiotics and surgery for source control; speciation and sensitivities of isolates taken during surgery will guide treatment. Infections are typically polymicrobial and the major pathogens involved are usual residents of the gastrointestinal tract, including Enterobacteriaceae, Streptococci, and anaerobes.	• cIAI and cUTI are serious bacterial infections that can cause significant morbidity. Both infections may progress to sepsis and death despite appropriate management.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• cUTI occurs in pediatric patients with underlying urological abnormalities; these abnormalities may lead to recurrent infections that may be difficult to treat, especially if the patient is exposed to multiple courses of antibacterial drugs that select for drug-resistant organisms. Infections are generally caused by Gram-negative organisms, such as Enterobacteriaciae or *Pseudomonas*.	
Current Treatment Options	• There are limited treatment options for cIAI and cUTI in pediatric patients caused by certain Gram-negative pathogens, such as carbapenem-resistant Enterobacteriaciae (CRE). • AVYCAZ requires the addition of metronidazole for anaerobic coverage, and often additional Gram-positive coverage for organisms such as *Enterococcus* in cIAI.	• There is a need for new antimicrobials to treat infections with MDR organisms in pediatric patients, particularly ESBL and carbapenemase producing organisms. • AVYCAZ offers an important treatment option for pediatric patients with cIAI and cUTI. Avibactam protects ceftazidime against degradation by a range of beta-lactamase producing organisms.
Benefit	• The primary endpoint of the trials was to establish safety and tolerability of CAZ-AVI in pediatric patients. Efficacy was a secondary endpoint, and the studies were not powered for statistical inference testing. • For Study D4280C00015 (cIAI), the clinical response rate in the ITT population was 56/61 (91.8%) for AVYCAZ, and 21/22 (95.5%) for meropenem. • For Study D4280C00016 (cUTI), the combined clinical and microbiologic response rate in the micro-ITT population was 39/54 (72.2%) for AVYCAZ and 14/23 (60.9%) for cefepime.	• Efficacy has been established in adult populations for cUTI and cIAI. As the course of the disease and the effects of the drug are sufficiently similar in in adults and pediatric patients, efficacy can be extrapolated from adults to pediatric patients. Two pediatric studies, one each in cUTI and cIAI, provide supportive evidence of AVYCAZ efficacy for pediatric

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		patients aged ≥3 months to 18 years. • The PK results from the clinical trials demonstrate that the exposure in pediatric patients with cIAI and cUTI at the proposed doses is reasonably similar to the exposure in adult patients receiving the approved dose. The results of the probability of pharmacokinetic-pharmacodynamic (PK-PD) target attainment (PTA) analysis also provide supportive evidence of effectiveness.
Risk	• Safety concerns are described in the current AVYCAZ labeling based upon experiences in the adult population with cIAI, cUTI, and HABP/VABP. The currently labeled range of adverse effects are consistent with an antibacterial drug of the cephalosporin class. The most serious adverse events include hypersensitivity reactions, *C. difficile* associated diarrhea, and central nervous system reactions. • There were no deaths in the pediatric studies, but 3 discontinuations due to adverse events occurred in pediatric patients treated with AVYCAZ. The causality of AVYCAZ to these adverse events resulting in discontinuation is not clear. • Treatment Emergent Adverse Events (TEAEs) in the pediatric studies occurred at a similar rate in subjects who received AVYCAZ (53.1%) as compared to those who received a comparator treatment (56.0%). The only AE occurring in more than 5% of pediatric patients was vomiting. • There was a decreased clinical response in adult patients with cIAI	• The safety profile in pediatric patients was comparable to the previously established safety profile in adults. • The most serious potential adverse events in the adult population, as described in the AVYCAZ package insert, were not observed in the pediatric population most likely due to the small size of the study population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with rapidly improving renal function. This is described as a warning in the current AVYCAZ labeling. There were few pediatric patients with renal impairment enrolled in the pediatric studies.	
Risk Management	• There were no new safety signals in the pediatric population studied, therefore no new warnings are recommended. • There are no new safety signals in post-marketing reports.	• The risks associated with AVYCAZ use in the pediatric population are comparable to that of the adult population. These risks will be communicated in appropriate sections of labeling, including the Adverse Reactions sections of the package insert. Routine postmarketing surveillance activities will suffice at this point. There are no safety signals/potential for safety issues that require a Risk Evaluation and Mitigation Strategy (REMS) at this time.

1.4. Patient Experience Data

In both studies, a blinded observer performed clinical assessments of the treatment response and causality of adverse events in the pediatric patients. This included an assessment of patient symptoms, which depended on the age of the patient.

2 Therapeutic Context

2.1. Analysis of Condition

The most likely etiology of cIAI in pediatric patients depends on the patient's age and existing comorbidities. cIAI is usually treated with a combination of antibiotics and surgery for source control; speciation and sensitivities of isolates taken during surgery will guide treatment, but infections are typically from the gut flora and are polymicrobial in nature. cUTI is common in pediatric patients with underlying urological abnormalities. These abnormalities may lead to recurrent infections that are more difficult to treat, especially if the patient is exposed to multiple courses of antibiotics that select for resistant organisms. In addition, frequent hospitalizations increase the risk for acquiring resistant organisms. Even patients without exposure to antibiotics or healthcare settings may be at risk for acquiring infections with resistant organisms if they are prevalent in the community. Consequently, expansion of the treatment armamentarium is necessary to combat infections caused by a range of beta-lactamase producing Gram-negative organisms as resistance phenotypes emerge and evolve.

2.2. Analysis of Current Treatment Options

The following tables provide an extensive list of therapeutic options for cIAI and cUTI, with comments indicating whether the drugs are approved or used off-label for pediatric patients.

Table 2: Therapeutic options for cUTI

Generic name	Trade name	Comments
Extended-spectrum penicillins		
Piperacillin	Pipracil	Approved for UTI; used off-label in pediatrics
Cephalosporins : Parenteral 2nd, 3rd and 4th generation		Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli Pediatric indications exist for cefoxitin (>3 months), cefuroxime (>3 months), cefotaxime (from birth), ceftazidime (from birth), ceftriaxone (>28 days), cefepime (>2 months)
Cefotetan	Cefotan	
Cefoxitin	Mefoxin	
Cefuroxime sodium	Zinacef	

Cefotaxime	Claforan	
Ceftazidime	Fortaz, Tazicef	
Ceftriaxone	Rocephin	
Cefepime	Maxipime	
β-lactam/β-lactamase Inhibitor Combinations		Timentin is approved for pediatric patients >3 months but is discontinued Zosyn is used off-label for cUTI in adults and children; Zerbaxa and Avycaz are not yet approved in pediatrics
Ticarcillin clavulanate	Timentin	
Piperacillin-tazobactam	Zosyn	
Ceftolozane-tazobactam	Zerbaxa	
Ceftazidime-avibactam	Avycaz	
Fluoroquinolones		Levaquin is used off-label in pediatrics for cUTI Ciprofloxacin is approved from age 1 for cUTI Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy
Levofloxacin	Levaquin	
Ciprofloxacin	Cipro	
Carbapenems		Meropenem alone is used off-label for cUTI in adult and pediatric patients Pediatric indications exist for primaxin (approved from <1 week of age) and ertapenem (>3 months) Doripenem has been discontinued
Imipenem-cilastatin	Primaxin	
Ertapenem	Envanz	
Doripenem	Doribax	
Meropenem-vaborbactam	Vabomere	
Monobactams		Approved from 9 months of age Although used in pts with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime
Aztreonam	Azactam	
Aminoglycosides		Pediatric indications exist for gentamicin (from age 1 week or less), amikacin (from birth), tobramycin (from age 1 week or less) Gentamicin, amikacin and tobramycin are not indicated in uncomplicated initial episodes of urinary tract infections unless the causative organisms are not susceptible to antibiotics having less potential toxicity. Risk of nephrotoxicity and ototoxicity.
Gentamicin		
Amikacin		
Tobramycin		
Plazomicin	Zemdri	
Tetracyclines		Minocycline is not recommended under age 8
Minocycline	Minocin	
Polymyxins		Polymyxin B and Colistimethate have pediatric indications from infancy 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	
Trimethoprim-Sulfamethoxazole	Bactrim	Contraindicated under age 2 months; IV formulation for "severe UTI"

Table modified from the original review of NDA 206494 by Dr. Benjamin Lorenz

Table 3: Therapeutic options for cIAI

Generic name	**Trade name**	**Comments**
Extended-spectrum penicillins		No pediatric indication
Piperacillin	Pipracil	
Cephalosporins (parenteral 2nd, 3rd and 4th generation)		Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli Pediatric indications exist for cefoxitin (>3 months), cefuroxime (>3 months), cefotaxime (from birth), ceftazidime (from birth), ceftriaxone (>28 days), cefepime (>2 months)
Cefotetan	Cefotan	
Cefoxitin	Mefoxin	
Cefotaxime	Claforan	
Ceftazidime	Fortaz, Tazicef	
Ceftriaxone	Rocephin	

Cefepime	Maxipime	
β-lactam/β-lactamase Inhibitor Combinations		Timentin is approved for pediatric patients >3 months but is discontinued Unasyn is used off-label for IAI in pediatric patients; Zerbaxa and Avycaz are not yet approved in pediatrics Zosyn is approved from 2 months of age
Ticarcillin clavulanate	Timentin	
Ampicillin-sulbactam	Unasyn	
Piperacillin-tazobactam	Zosyn	
Ceftolozane-tazobactam	Zerbaxa	
Ceftazidime-avibactam	Avycaz	
Fluoroquinolones		Ciprofloxacin is used off-label for IAI in pediatrics Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy
Ciprofloxacin	Cipro	
Moxifloxacin	Avelox	
Carbapenems		Pediatric indications exist for primaxin (approved from <1 week of age), meropenem (from <2 weeks) and ertapenem (>3 months) Doripenem has been discontinued
Imipenem-cilastatin	Primaxin	
Meropenem	Merrem	
Ertapenem	Envanz	
Doripenem	Doribax	
Monobactams		Approved from 9 months of age 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		Pediatric indications exist for gentamicin (from age 1 week or less), amikacin (from birth), tobramycin (from age 1 week or less)
Gentamicin		
Amikacin		
Tobramycin		
Tetracyclines		Vancomycin-resistant *Enterococcus faecium* (VREF) activity, but *Pseudomonas aeruginosa* is intrinsically resistant to tigecycline Both approved in adults only; pediatric dosing recommendations are given for tigecycline in the case that no alternative drug exists
Tigecycline	Tygacil	
Eravacycline	Xerava	
Polymyxins		Approved from infancy 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	Approved from infancy
Metronidazole	Flagyl	Used off-label in pediatrics. Used in combination with other agents (ex. Cephalosporins) for anaerobic coverage
Linezolid	Zyvox	Approved for VRE in adults and pediatrics; not specifically for cIAI

Table modified from the original review of NDA 206494 by Dr. Benjamin Lorenz

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

AVYCAZ was initially approved in February 2015 for the treatment of adults with cUTI and cIAI in patients with limited or no alternative treatment options. Due to the limited clinical data submitted in the original application, the drug was approved with a statement of limited use. Two subsequent efficacy supplements provided clinical trial data to support the removal of the limited use statements. The efficacy supplement for cIAI was approved on June 22, 2016 (Supplement 2) and cUTI on January 26, 2017 (Supplement 3). The efficacy supplement for HABP/VABP was approved on February 1, 2018 (Supplement 4). The dosing of AVYCAZ is the same across indications for adults aged 18 or more years, namely 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) every 8 hours by intravenous (IV) infusion over 2 hours. The dose is modified for patients with impaired renal function.

This efficacy supplement proposes to add a new population, treatment of cIAI and cUTI in pediatric patients aged ≥3 months to 18 years. The supplement was submitted in response to Pediatric Research Equity Act (PREA) post-marketing requirements (PMR) 2862-1 (cUTI) and 2862-2 (cIAI) for the initial AVYCAZ NDA. The Applicant met the dates set for study completion (September, 2017) and sNDA submission (September, 2018).

3.2. Summary of Presubmission Regulatory Activity

A summary of the regulatory activity related to the submission of this sNDA is presented in

Table 4, below. These studies were submitted as part of the PMRs from the original NDA. There were several protocol modifications to facilitate the enrollment of patients less than 6 years of age (cohorts 3 and 4).

Table 4: Regulatory history of pediatric sNDA submission

Date	Meeting/Correspondence
04 Jun 2015	The clinical study report for Study D4280C00014, the first study with CAZ-AVI in pediatric patients, was submitted to IND 101,307 (Serial No. 0161).
22 Jun 2015	The initial protocols for Studies D4280C00015 (PMR 2862-2) and D4280C00016 (PMR 2862-1) in cIAI and cUTI, respectively, were submitted to the IND (Serial No. 0163), along with a dose rationale document summarizing the results of Study D4280C00014, population PK model development, simulations of dose regimens, and proposed dose recommendations for Cohorts 1 and 2 as agreed with the EMA Pediatric Committee (PDCO). Doses for Cohorts 3 and 4 were under review at the time of submission.
18 Nov 2015	Amended protocols for Studies D4280C00015 and D4280C00016, which included the doses for Cohorts 3 and 4 approved by PDCO, were submitted to the IND (Serial No. 0174).
30 Aug 2016	Allergan received comments from the FDA on 01 Jul 2016, relating to the study design and analysis of PREA PMR Studies D4280C00015, and D4280C00016. Allergan responded to the comments on 30 Aug 2016 (Serial No. 0200) providing for justification of the sample size for Cohort 4 and agreeing to FDA's recommendations on study design.
03 Mar 2017	For Studies D4280C00015 and D4280C00016, Allergan proposed that the minimum required number of evaluable patients in Cohorts 3 and 4 be achieved by recruiting the total in these cohorts across both studies combined. This proposal was initially submitted in a Type C meeting request on 21 Nov 2016. The FDA agreed to the modifications on 03 Mar 2017, which were then submitted as a protocol amendment (Serial. No. 0212) on 06 Apr 2017.
01 Sep 2017	The sponsor proposed to replace the requirement for a minimum number of 24 evaluable patients in Cohort 3 for the pooled safety analysis of data from Studies D4280C00015 and D4280C00016 with a revised minimum number target of 22 evaluable patients to align with the numbers of patients recruited to date. The proposal was submitted to the IND (Serial Number 0218) on 30 Jun 2017. The sponsor received agreement from FDA on 1 September 2017 to allow for study completion according to PMR timelines.
02 Jul 2018	Type B pre-sNDA for the proposed pediatric cIAI and cUTI sNDA.

Source: Sponsor Table 2-1 from the Reviewer's Guide

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

At the site selection meeting on October 12, 2018 with OSI, it was determined that no inspections were necessary for this supplement. Several of the sponsor's sites had been previously inspected for earlier supplements in the NDA and appeared to be compliant with good clinical practices. In this supplement, the number of patients enrolled at each site was small and there were no anomalous findings regarding safety or efficacy identified at any particular site.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No
Sufficient controls to insure safety and efficacy of the commercial product: Yes

AVYCAZ is currently commercially available as an intravenous formulation for adults. The pediatric formulation is the same as the adult formulation. At the time of this review, there are no known product quality issues precluding the acceptability of AVYCAZ for use in pediatric patients.

4.3. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The only new nonclinical studies that were conducted for this NDA supplement were range-finding and definitive juvenile toxicology studies in rats.

The primary finding in both the range-finding and definitive juvenile toxicology studies was renal cysts that were detected as gross pathology and microscopically after the dosing period in both studies and at a lower incidence with evidence of reversal after the recovery period in the definitive study. In the microscopic analysis in the definitive study, the renal cysts occurred in both sexes in vehicle control animals as well as animals treated with CAZ-AVI, but with a slightly higher incidence in high-dose females. The absence of correlative changes in renal function or histopathology findings suggests the cysts were not toxicologically relevant in rats.

In both the range-finding and definitive juvenile toxicology studies, plasma AUC values for both ceftazidime and avibactam were reduced on PND 21 compared to PND 7. This finding is different than the toxicokinetic pattern for CAZ-AVI in other studies with adult rats where plasma AUC values for both compounds did not change with repeated dosing. Incomplete nephrogenesis[1] in very young rats may have influenced the toxicokinetic pattern exhibited in the juvenile toxicology studies. Because both compounds are primarily excreted in the kidney, excretion patterns could have changed over time in developing kidneys perhaps leading to increased renal clearance of both compounds as the rats matured.

Exclusive of the slight increase in renal cysts observed in high-dose CAZ-AVI females, the NOAEL values for the definitive juvenile toxicology study are the high doses of 455 mg/kg/day ceftazidime and 155 mg/kg/day avibactam. The human equivalent doses for these NOAEL values based on body surface area comparison are approximately equivalent to the maximum recommended daily doses of ceftazidime and avibactam in AVYCAZ (6 g ceftazidime/1.5 g avibactam per day). The results of the juvenile toxicity studies in rats do not suggest that serious adverse reactions are expected with clinical pediatric administration of AVYCAZ.

5.2. Referenced NDAs, BLAs, DMFs

The study summary and review information regarding the submitted nonclinical pharmacology and toxicology studies for the initial application and approval of AVYCAZ can be found in the Pharmacology/Toxicology NDA Review and Evaluation for NDA 206494 by Wendelyn J. Schmidt, Ph.D. in DARRTS (2/18/2015).

[1] Zoetis, T, 2003, Species Comparison of Anatomical and Functional Renal Development, Birth Defects Research, (part B), 68:111-120.

5.3. Pharmacology

No new pharmacology studies were submitted.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
TK data from general toxicology studies *Juvenile Toxicology Study* *Combination (ceftazidime/avibactam; CAZ/AVI) toxicology study in juvenile rats* *Study Title: CAZ-AVI: 14 Day Intravenous Toxicity Study in Neonatal Rats with a 5-week Recovery Period, Study No.: 20047213*	Rat *$T_{1/2}$: Not determined* *Accumulation: Plasma AUC values for both ceftazidime and avibactam decreased 2- to 3-fold with repeated dosing. Plasma C_{max} values for ceftazidime increased 17-49% with repeated dosing. Plasma C_{max} values for avibactam remained the same or increased up to 27% with repeated dosing.* *Dose proportionality: Ceftazidime and avibactam plasma C_{max} and AUC values increased in a roughly dose-proportional manner.*

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: ***CAZ-AVI: 14 Day Intravenous Toxicity Study in Neonatal Rats with a 5-week Recovery Period****/ Study No.: 20047213*

Key Study Findings

- Histology findings in the Main Study included minimal renal cysts that were similar in incidence in control and CAZ-AVI treated males and low- and mid-dose females with a slightly higher incidence in high-dose females. After the 5-week recovery period, the incidence of renal cysts was lower in control and high-dose animals indicating partial reversibility, but the highest incidence still occurred in high-dose females.

- Other CAZ-AVI-related histology findings included fully reversible liver and spleen extramedullary hematopoiesis as well as a low incidence of focal peritubular fibrosis and tubular basophilia in the kidney that were only apparent in recovery animals.
- Unlike the toxicokinetic pattern observed in adult animals in other studies with ceftazidime or avibactam, plasma AUC values for both compounds decreased with repeated dosing in juvenile animals. The toxicokinetic pattern in this study was the same as that occurring in the range-finding study in juvenile rats.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Once per day: Vehicle control (Group 1), CAZ/AVI: 50/13 mg/kg/day (Group 2), CAZ/AVI: 150/38 mg/kg/day (Group 3), CAZ/AVI: 455/115 mg/kg/day (Group 4)
Route of administration:	Intravenous bolus injection via the lateral tail vein
Formulation/Vehicle:	Sterile water of Injection, USP
Species/Strain:	Crl:CD(SD) Sprague-Dawley rat
Number/Sex/Group:	Main Study: 10/sex/group; Recovery Study: 10/sex/group for Groups 1 and 4
Age:	Postnatal day (PND) 7 at the start of dosing
Satellite groups/ unique design:	Neonatal Sprague-Dawley rats were administered vehicle (0.9% sodium chloride) or CAZ-AVI (50/13, 150/38, and 455/115 mg/kg/ day) in bolus intravenous injections into the lateral tail vein from postnatal days (PNDs) 7 to 20 before euthanasia and necropsy on PND 21 for Main Study animals. Recovery Study animals were dosed according to the same schedule as the Main Study animals, then maintained without dosing until necropsy on PND 56. Toxicokinetic animals were also dosed and blood samples were obtained at different timepoints on PNDs 7 and 20.
Deviation from study protocol affecting interpretation of results:	Yes; multiple deviations in the study protocol occurred, but the deviations were not considered to have altered the study results or the integrity of the study.

Observations and Results: changes from control

Parameters	Major findings
Mortality	No CAZ-AVI-related deaths occurred in the study.
Clinical Signs	No CAZ-AVI-related clinical signs were observed.
Body Weights	There were transient reductions in the mean body weight gain between PND 8 and 12 in males and PND 7 and 12 in females in the all the CAZ-AVI groups compared to control values. The only significant reductions in body weight gain occurred in HD males on PNDs 8, 10, and 11 (-29%, -21%, and -25% respectively) and in HD females on PNDs 8, 11, and 12 (-26%, -16%, and -21% respectively). Beginning on PND 14, the mean body weight gains in both sexes in all CAZ-AVI dosed groups were increased over the control group. In addition, during the dosing phase, the mean body weights in HD males were significantly reduced on PND 12 (-10.2%) and PND 13 (-8.5%) compared to controls. Body weights and body weight gains for both sexes during the recovery period were generally comparable between the control and HD groups.
Hematology	No CAZ-AVI-related changes in hematology parameters were observed.
Clinical Chemistry	Significant but low magnitude changes in some serum chemistry parameters occurred in Main Study animals. Triglyceride levels were significantly reduced in HD males (-64%) and MD and HD females (-55% and -67% respectively) compared to control values. Alkaline phosphatase was significantly decreased in a dose-dependent manner in LD, MD, and HD males (-16%, -20%, and -23% respectively) and in HD females (-28%). Serum potassium was significantly increased in CAZ-AVI treated MD and HD males (+11% and +10% respectively) and females (+8% and +7% respectively). After the Recovery Period, serum values for triglycerides, alkaline phosphatase, potassium, and alanine transferase were similar in control and HD animals.
Urinalysis *[delete the row if not evaluated]*	No CAZ-AVI-related changes in any urinalysis parameters were observed.
Gross Pathology	A low incidence of cysts in the right and left kidney were detected in males and females in the LD (2/20) and MD

	3/20) CAZ-AVI groups, but not in HD animals. After the recovery period, both control (3/20) and HD (6/20) males and females exhibited renal cysts, but the incidence was increased in HD dose animals. In recovery HD males (2/10) and females (3/10) but not control animals, depressed areas or pitted renal surfaces were noted.
Organ Weights	There were no CAZ-AVI-related changes in the weights of the brain, paired kidneys, or spleen (the only organs that were weighed) in the males or females in any dose group at the end of the dosing period (PND 21) and the end of the recovery period (PND 56).
Histopathology **Adequate battery:** Yes	The administration of CAZ-AVI to juvenile rats resulted in a higher incidence of increased extramedullary hematopoiesis (EMH) in the spleen and liver of HD animals of both sexes in the Main Study. In the liver, minimal liver EMH was observed in 2/10 and 3/10 males and 1/10 and 5/10 females in the control and HD groups respectively. Similarly, EMH in the spleen was observed in 1/10 and 5/10 males and 1/10 and 7/10 females in the control and HD groups respectively. Liver and spleen EMH was similar to control values for LD and MD animals. After the recovery period, EMH in liver and spleen was no longer present in control or HD males and females indicating full reversibility of this effect. Renal cysts were present in control and CAZ-AVI dosed animals of both sexes. The cysts were morphologically similar and showed a similar pattern of distribution in both control and CAZ-AVI dosed animals. However, the incidence of cysts was slightly higher in females of all CAZ-AVI dosed groups compared to the control group. In the control, LD, MD, and HD groups, minimal renal cysts were detected in 6/10, 6/10, 7/10, and 5/10 males and 4/10, 6/10, 8/10, and 7/10 females respectively. After the recovery period, renal cysts were present in control and HD animals of both sexes at a lower incidence than in Main Study animals. The incidence of the cysts was slightly increased in the HD animals compared to control animals. Minimal renal cysts were observed in 2/10 and 3/10 males and 1/10 and 3/10 females in the control and HD groups respectively after the recovery period.

	Minimal focal peritubular fibrosis in the kidney of recovery animals was present at a low incidence in both control and HD animals of both sexes. The incidence was similar in HD and control males, but occurred at a higher incidence in HD females. Focal peritubular fibrosis was observed in 4/10 and 3/10 males and 1/10 and 4/10 females in the control and HD groups respectively after the recovery period. This effect may have occurred secondary to cyst formation and resolution.
[Other evaluations]: **Functional Observational Batter (FOB)**	FOB measurements were obtained 8 days after the end of dosing. No overt neurobehavioral alterations (e.g., tremors, convulsions, stereotypical movements, gait alterations or other abnormal movements) were observed in the FOB examinations.

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.
*: *[if the answer is "no" explain why the histopath battery is not adequate]*

General toxicology; additional studies
A range-finding juvenile toxicology study was also conducted in support of this supplemental submission for NDA 206494.

Study title: CAZ-AVI: 14 Day Intravenous Dose Range Finding Toxicity Study in Neonatal Rats. (Study No.: 20040271)

Methods

The range-finding study was conducted with the same strain of rats as the definitive study, Crl:CD(SD), with 4/sex/group and included the same control and dosing groups as the definitive study, vehicle control (saline), low dose CAZ-AVI (50/13 mg/kg/day), mid-dose CAZ-AVI (150/38 mg/kg/day), and high-dose CAZ-AVI (455/115 mg/kg/day). Animals were dosed once per day by intravenous bolus injection for two weeks from postnatal day (PND) 7 to PND 20 with animal necropsy and terminal measurements performed on PND 21. No recovery period was included in this study.

Results

1. No CAZ-AVI-related mortality, clinical signs, or body weight loss were observed.
2. On PND 21, serum gamma glutamyltransferase (GGT) levels were reduced by up to 100% in a CAZ/AVI dose-dependent manner in both males and females. Serum triglyceride levels were reduced in high-dose males by 30% and total protein, albumin,

and globulin were respectively reduced in males by 13.7, 8.1, and 22.4% and in females by 13.8, 7.6, and 23.3% compared to control values.

3. Food consumption and hematology and urinalysis parameters were not assessed.
4. The incidence of renal cysts was slightly increased in CAZ/AVI-treated animals, but not in a dose-dependent manner and renal cysts also occurred in control animals.
5. Minimal unilateral or bilateral tubular dilation and vacuolation in the renal cortex sometimes accompanied the renal cysts, but no other functional or structural kidney changes were observed.
6. Unlike the toxicokinetic pattern observed in adult animals in other studies with ceftazidime or avibactam, plasma AUC values for both compounds decreased with repeated dosing in juvenile animals. This is the same pattern that was observed in the definitive juvenile toxicology study.

5.5.2. Genetic Toxicology

No new genetic toxicology studies were submitted.

5.5.3. Carcinogenicity

No new carcinogenicity studies were submitted.

5.5.4. Reproductive and Developmental Toxicology

No new reproductive and developmental toxicology studies were submitted.

5.5.5. Other Toxicology Studies

No other nonclinical toxicology studies were submitted.

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology reviewed the information contained in supplemental NDA 206,494 S-005. The clinical pharmacology information submitted in this supplement NDA supports the approval of AVYCAZ™ (ceftazidime-avibactam, CAZ-AVI) for the treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) in pediatric patients 3 months of age and older. See Table 5 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 5. Summary of OCP Recommendations & Comments on Key Review Issues.

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>Pivotal or supportive evidence of effectiveness</td><td>The pivotal evidence of effectiveness of CAZ-AVI in the treatment of adult patients with cIAI and cUTI was provided in previous submissions of NDA 206,494.

Three clinical trials in pediatric patients provide supportive evidence of effectiveness. Because cIAI and cUTI are assumed to be pathophysiologically similar in adults and children, the effective exposure of CAZ-AVI in adults is predicted to be effective in children as well. The PK results from the three clinical trials combined with adult PK data demonstrate that the exposure in pediatric patients with cIAI and cUTI at the proposed doses (see below) is reasonably similar to the exposure in adult patients receiving the approved dose. The results of the probability of pharmacokinetic-pharmacodynamic (PK-PD) target attainment (PTA) analysis also provide supportive evidence of effectiveness.</td></tr>
<tr><td>General dosing instructions</td><td>The recommended dosing regimen of CAZ-AVI is shown in the table below:
<table>
<tr><th>Age Range</th><th>Dosing recommendation</th></tr>
<tr><td>6 months to <18 years with eCrCl greater than 50 mL/min/1.73 m^2</td><td>Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg to a maximum dose of ceftazidime 2 grams and avibactam 0.5 grams administered every 8 hours by IV infusion</td></tr>
<tr><td>3 months to <6 months</td><td>Ceftazidime 40 mg/kg and avibactam 10 mg/kg administered every 8 hours by IV infusion</td></tr>
</table>
eCrCl: estimated creatinine clearance as calculated using the bedside Schwartz equation

The infusion duration is 2 hours. The recommended treatment duration is 5-14 days and 7-14 days for cIAI and cUTI including pyelonephritis, respectively.</td></tr>
</table>

<table>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>The following AVYCAZ dosage is recommended in pediatric patients 2-17 years with renal impairment.
<table>
<tr><th>Estimated Creatinine Clearance (mL/min/1.73m^2)[a]</th><th>Recommended Dosage Regimen for AVYCAZ (ceftazidime and avibactam)[b]</th></tr>
<tr><td>31 to 50</td><td>Ceftazidime 25 mg/kg and avibactam 6.25 mg/kg up to a maximum dose of ceftazidime 1 grams and avibactam 0.25 grams every 8 hours</td></tr>
<tr><td>16 to 30</td><td>Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg up to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams every 12 hours</td></tr>
<tr><td>6 to 15</td><td>Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg up to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams every 24 hours</td></tr>
<tr><td>Less than or equal to 5[c]</td><td>Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg up to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams every 48 hours</td></tr>
</table>
a eCrCl as calculated using the bedside Schwartz equation
b All doses of AVYCAZ are administered over 2 hours
c Both ceftazidime and avibactam are hemodialyzable; thus, administer AVYCAZ after hemodialysis on hemodialysis days</td></tr>
<tr><td>Labeling</td><td>The Applicant’s proposed labeling requires edits in the following sections:
Dosage and Administration: Update to the recommended dosage
Use in Specific Populations: Update to information about pediatric patients with renal impairment
Clinical Pharmacology: Update to subsection regarding pediatric patients</td></tr>
</table>

6.2. Clinical Pharmacology Questions

6.2.1. Is the proposed dosing regimen appropriate for the general pediatric patient population for which the indication is being sought? What supportive evidence of effectiveness and safety does the clinical pharmacology program provide?

Yes, the Applicant’s proposed dose (See Table 5) is appropriate for the treatment of pediatric patients 3 months-17 years with cIAI and cUTI based on the comparable plasma exposures of CAZ and AVI in pediatric patients receiving the proposed dose relative to that in adult patients receiving the approved dose (i.e., extrapolation of efficacy from adult patients to pediatric patients), the efficacy and safety data from clinical studies conducted in pediatric patients, and the results of probability of PK/PD target attainment. The summary of this information is provided below.

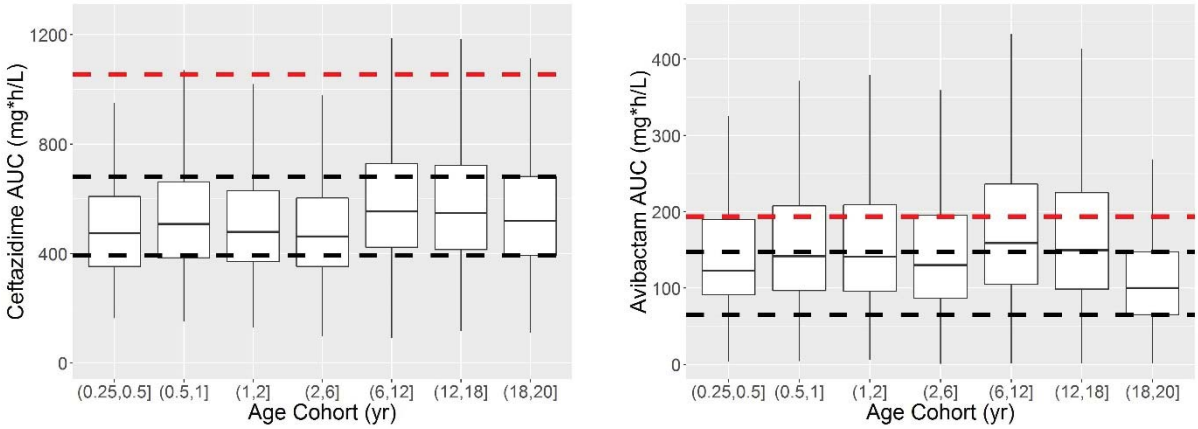
Full Extrapolation of Efficacy from Adult Patients to Pediatric Patients

The primary evidence of effectiveness is provided by the finding that plasma exposure (using AUC as an exposure metric) of CAZ and AVI in pediatric patients at the proposed dose is reasonably similar to exposure of CAZ and AVI in adult patients with cIAI and cUTI receiving the approved dose, in which CAZ-AVI was shown to be effective. Because cIAI and cUTI are assumed to be pathophysiologically similar in adults and children, the effective exposure of CAZ-AVI in adults is predicted to be effective in children. Thus, efficacy in cIAI and cUTI can be fully extrapolated from adults to pediatrics if the exposure in pediatric and adult patients are comparable. To collect PK, efficacy, and safety data, three studies were conducted in pediatric patients:

- D4280C00014 in patients with suspected or confirmed infection
- D4280C00015 in patients with cIAI
- D4280C00016 in patients with cUTI

PK data from each study were used to build population PK models, which were then used to simulate exposure of CAZ and AVI at the proposed dose. The results of this simulation were used to evaluate whether the exposure in pediatric patients receiving the propose dose is reasonably similar to that in adult patients receiving the approved dose. The predicted AUC of CAZ and AVI in pediatric patients and adult patients (18 to 20 years) at the proposed dose on Day 2 is illustrated in Figure 1.

Figure **1**. AUC of CAZ (left panel) and AVI (right panel) on Day 2 Following Administration of the Proposed Dose of CAZ-AVI in Simulated cIAI Patients with Normal Renal Function Stratified by Age.



Normal renal function is defined as a creatinine clearance of 81-150 mL/min/1.73m^2 estimated by the bedside Schwartz equation in pediatric patients and the BSA-normalized Cockcroft-Gault equation in adult patients. The black dashed lines represent the 25th and 75th percentile of AUC in adult patients with normal renal function and is used as an efficacy reference. The red dashed line represents the 75th percentile of AUC in adult patients with mild renal impairment (51-80 mL/min/1.73m^2). The red line is used as a safety reference because patients with mild renal impairment experience a higher exposure of CAZ and AVI, but both agents are considered safe without any dose adjustments in this patient subpopulation.

Table 6 lists the AUCs of CAZ and AVI and fold changes of AUCs relative to adult patients with normal renal function.

Table 6. Geometric Mean AUCs of CAZ and AVI on Day 2 Following Administration of the Proposed Dose of CAZ-AVI in Simulated cIAI Patients with Normal Renal Function and Fold Change of AUC in Pediatric Patients Relative to Adult Patients.

Age (years)	Ceftazidime		Avibactam	
	Mean AUC (mg*hr/L)	Fold Change*	Mean AUC (mg*hr/L)	Fold Change*
0.25-0.5	581.1	1.0	128.5	1.3
0.5-1	614.8	1.0	143.1	1.5
1-2	560.0	0.9	138.6	1.5
2-6	554.9	0.9	129.5	1.4
6-12	658.2	1.1	157.1	1.6
12-18	653.3	1.1	145.9	1.5
18-20	**609.8**	**1.0**	**95.4**	**1.0**

*Fold change in AUC relative to adult patients with normal renal function (81-150 mL/min/1.73m^2). The values of AUC in adult patients (18-20, highlighted in yellow and bolded) are used as an efficacy reference.

The AUCs of CAZ and AVI following administration of the proposed dose in all age cohorts appeared to be reasonably similar to or higher than the efficacy reference (AUCs of CAZ and AVI in adult patients with normal renal function, 81-150 mL/min/1.73m^2). Thus, the achieved exposure of CAZ and AVI in pediatric patients is considered to be effective. The AUCs of CAZ and AVI appear to be similar to or under the safety reference (AUCs of CAZ and AVI in adult patients with mild renal impairment, 51-80 mL/min/1.73m^2). Only patients with cIAI are described in this review because the AUCs in patients with cUTI and cIAI are similar with a trend towards higher AUCs in patients with cUTI relative to those in patients with cIAI. Patients 18-20 years are used as a representative for adult exposure because exposure is not expected to differ in adults by age, except for changes due to renal function. Exposure on Day 2 is used as a surrogate for steady-state exposure based on relatively short half-lives of CAZ and AVI (i.e., <3 hours).

At the proposed doses, the AVI AUC, but not the CAZ AUC, in pediatric patients tends to be higher than that in adult patients after accounting for bodyweight. This is because the bodyweight-adjusted clearance of AVI in pediatric patients with cIAI was lower than that in adult patients with cIAI by approximately 15%. However, this difference was not observed in the clearance of CAZ. CAZ-AVI is supplied in a fixed dose ratio (i.e., 4:1). Thus, it would not be possible to maintain comparable AUCs of both AVI and CAZ in pediatric and adult patients with cIAI. Although the proposed dose of CAZ-AVI may result in a higher AUC of AVI in pediatric patients than that in adult patients receiving the approved dose, there were no serious adverse events observed in clinical studies conducted with the proposed pediatric dose. Collectively, the proposed pediatric CAZ-AVI dose is considered to provide pediatric patients with the exposure of CAZ and AVI comparable to or slightly higher than those in adult patients receiving the approved dose without safety concerns.

Clinical Efficacy and Safety of CAZ-AVI in Pediatric Patients

Clinical response was >90% in patients treated with CAZ-AVI for both cUTI and cIAI. However, these studies were not statistically powered to show efficacy, and there were few or no patients in multiple age cohorts.

In these clinical studies, adverse events were low and similar between CAZ-AVI and the comparators, with the most common adverse event being vomiting. For further detailed review of the efficacy and safety results including the design of clinical studies, please see Section 7 and Section 9, respectively.

Probability of Pharmacokinetic-Pharmacodynamic Target Attainment Analysis

Additional supportive evidence of effectiveness is provided by the probability of PK-PD target attainment (PTA) analysis. The PK-PD targets for CAZ and AVI are 50% time that free CAZ concentration is above the MIC and 50% time that free concentration is above the concentration threshold (1 mg/L), respectively. As shown in Table 7, the dose proposed by the Applicant produces an exposure that meets or exceeds the PK-PD targets of CAZ and AVI up to an MIC of 8 mg/L, which is equivalent to the labeled in vitro susceptibility testing interpretation criteria (referred as "breakpoint" hereafter) for CAZ-AVI in adults with cIAI and cUTI. For further details, please see Section 15.4.3. for a review of the PTA analysis.

Table 7. Joint CAZ-AVI PTA in Simulated Patients with cIAI and Normal Renal Function Following Administration of the Proposed Dose of CAZ-AVI on Day 2 at an MIC 8 mg/L.

Age (years)	Infusion Duration (hr)	
	2	3
0.25-0.5	89%	95%
0.5-1	84%	94%
1-2	78%	92%
2-6	77%	90%
6-12	86%	95%
12-18	91%	97%
18-20	89%	96%

There is >80% joint PTA with an infusion duration of 2 hr, except for patients 1-6 years. In this application, the >80% joint PTA is acceptable due to the conservative assumptions used in the process of estimating PTA. Essentially, the reviewer conducted the PTA analysis in a way that inflated the variability present in the model to represent a worst-case scenario (See Section 15.2.3 for details on how the reviewer conducted the PTA analysis).

On the other hand, patients 1-6 years administered the 2-hr infusion have a PTA <80% at an MIC of 8 mg/L while patients 1-6 years administered the 3-hr infusion have a PTA $\geq$90%. The review team considered recommending a higher infusion duration in this patient subpopulation

but ultimately decided against it. In many situations, it would be clinically infeasible to wait until after the in vitro susceptibility report containing the MIC is finalized and delivered to start therapy with CAZ-AVI. Additionally, the PK-PD targets for CAZ and AVI were selected to produce a 2-$\log_{10}$ decrease in bacterial counts, which may be more than is necessary for successful treatment of cIAI or cUTI.

Additionally, this review focuses on patients with cIAI because the exposures of CAZ and AVI are higher in patients with cUTI relative to patients with cIAI. Accordingly, the PTA in pediatric patients with cUTI will be greater than the PTA in pediatric patients with cIAI.

Of note, in the Statistical Reviewer's integrated analysis, the clinical cure rate was lower patients 12-17 years in the CAZ-AVI arm relative to the comparator arm (See Section 7). However, there does not appear to be a clear trend between exposure and response in pediatric patients, in part due to the limited number of patients who experienced treatment failure. Additionally, AUC and PTA in patients 12-17 years are predicted to be similar to or higher than those in adults. Thus, the lower clinical cure in patients 12-17 years relative to the comparator arm is likely not related to the exposure or dose of CAZ-AVI.

6.2.2. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes, an alternative dosing regimen is required in pediatric patients with renal impairment.

In general, for drugs eliminated exclusively by renal excretion, the effect of renal impairment on the PK of those drugs is evaluated in adult subjects with renal impairment and, as needed, dose adjustments in adult patients with renal impairment are described in the labeling. Although it is presumed that renal impairment may also affect the PK of those drugs in pediatric patients, dose adjustments in pediatric patients with renal impairment are not commonly evaluated and are not described adequately in the product labeling.

In this submission, the Applicant evaluated and proposed a dose adjustment in pediatric patients with moderate renal impairment, defined as an eCrCl of 31-50 mL/min/1.73m^2. We conducted additional analyses and proposed additional dose adjustments in pediatric patients 2-17 years with eCrCl less than 30 mL/min/1.73 m^2 as shown in Table 5. The summary of these analyses and the rationale for recommended dose adjustment in pediatric patients with renal impairment are provided below.

<u>Pediatric Patients 2-17 years</u>
The Applicant proposes a 50% reduction in the dose in pediatric patients (2 to 17 years) with eCrCl in the range 31-50 mL/min/1.73m^2. This is the same as the recommended dose adjustment in adult patients with eCrCL in the range 31-50 mL/min. The AVYCAZ labeling

recommends additional dose adjustments for adult patients with more severe renal impairment(Table 8).

Table 8. Approved Dose of CAZ-AVI in Adult Patients with cIAI and cUTI Stratified by Creatinine Clearance.

Estimated Creatinine Clearance (mL/min)[a]	Recommended Dosage Regimen for AVYCAZ (ceftazidime and avibactam)[b] in Adult Patients
Greater than 50	AVYCAZ 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) every 8 hours
31 to 50	AVYCAZ 1.25 grams (ceftazidime 1 grams and avibactam 0.25 grams) every 8 hours
16 to 30	AVYCAZ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) every 12 hours
6 to 15[c]	AVYCAZ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) every 24 hours
Less than or equal to 5[c]	AVYCAZ 0.94 grams (ceftazidime 0.75 grams and avibactam 0.19 grams) every 48 hours

a As calculated using the Cockcroft-Gault formula.
b All doses of AVYCAZ are administered over 2 hours
c Both ceftazidime and avibactam are hemodialyzable; thus, administer AVYCAZ after hemodialysis on hemodialysis days.

According to the protocols of Studies D4280C00015 and D4280C00016, pediatric patients with renal impairment (including patients with eCrCl 31-80 mL/min/1.73m^2) could be enrolled in the studies and received reduced doses in alignment with the recommended dose adjustments for adult patients with renal impairment. However, as shown in Table 9, the pediatric clinical studies enrolled only 2 patients with eCrCl in the 31-50 mL/min/1.73m^2 range.

Table 9. Number of Enrolled Pediatric Patients Stratified by Baseline Normalized Creatinine Clearance and Age.

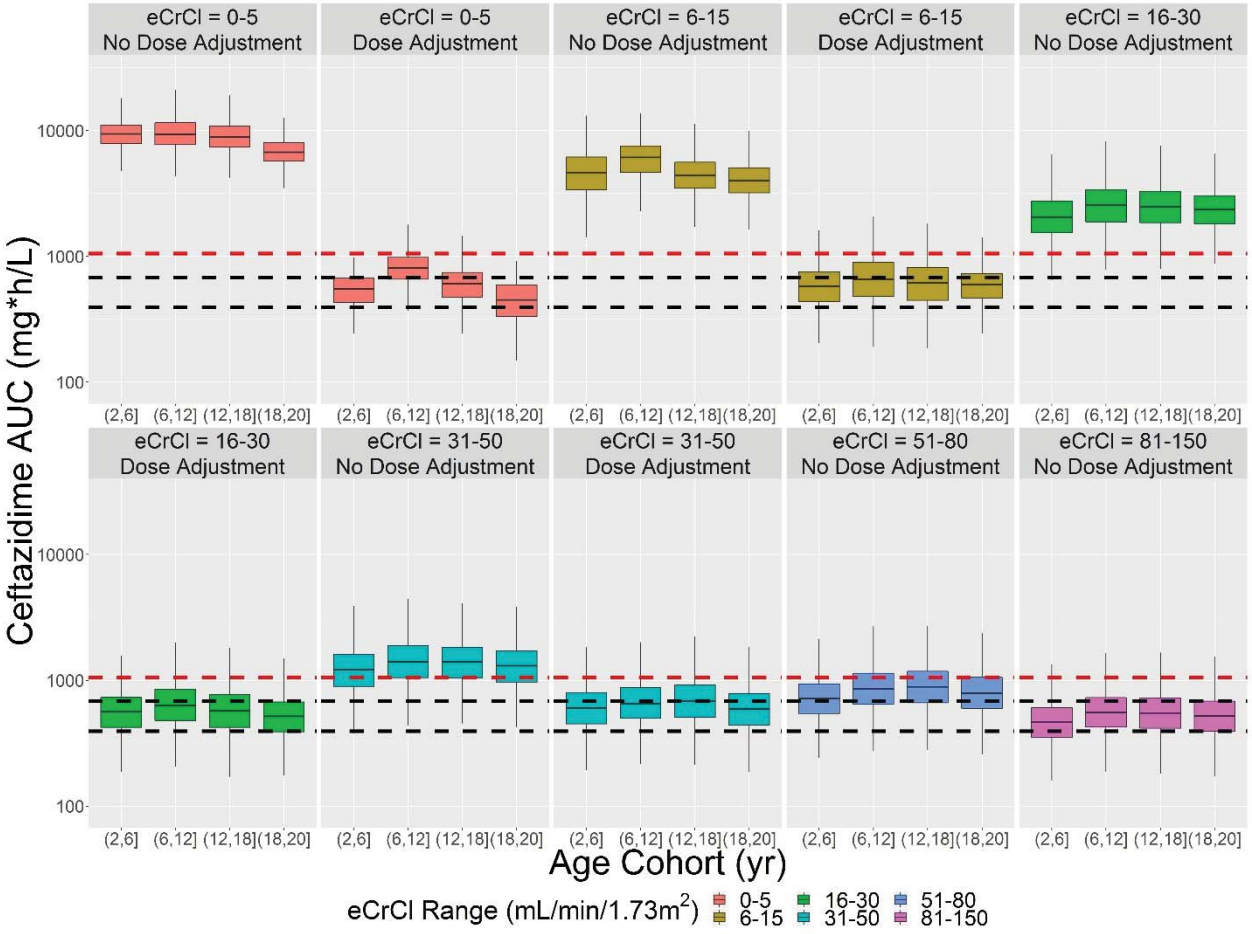
Age (years)	Normalized Creatinine Clearance (ml/min/1.73m^2)				
	0-30	31-50	51-80	81-120	>120
0.25-0.5	0	0	1	2	2
0.5-1	0	1	4	3	2
1-2	0	0	7	3	2
2-6	0	0	4	4	8
6-12	0	1	9	23	17
12-18	0	0	6	25	3

Accordingly, the population PK model, which was used to inform the dose and dose adjustment strategy for patients with renal impairment, was primarily built using adult data, and the covariate relationships (i.e., the relationship between creatinine clearance and drug clearance)

identified in adults were used in pediatric patients >2 years. Whether the relationship between creatine clearance on drug (i.e., CAZ and AVI) clearance in pediatric patients is similar to that in adult patients has not been validated. However, the assumption that the relationship between creatine clearance and drug clearance is the same in adult patients and pediatric patients after considering weight is physiologically reasonable.

Figure 2 and Figure 3 show the predicted values of AUC of CAZ and AVI, respectively, in adult (18-20 years in these analyses) and pediatric patients with varying degrees of renal function following administration of the proposed dose of CAZ-AVI (see Table 5) with and without dose adjustments for renal function proportional to the recommended adult dose adjustments for renal function (see Table 8).

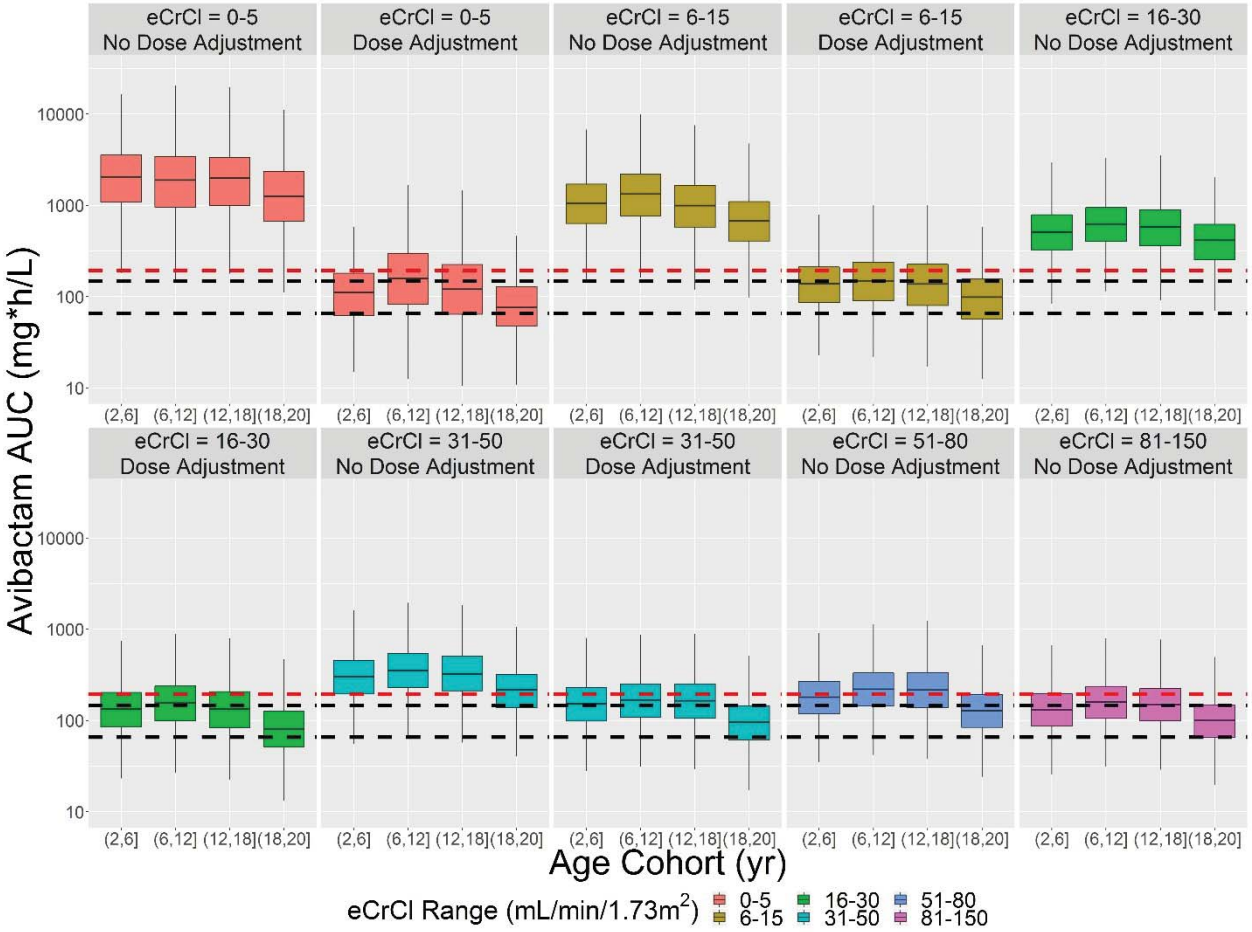
Figure 2. Ceftazidime AUC in Simulated Patients with cIAI with Varying Renal Function Administered the Proposed Dose of Ceftazidime with and without Dose Adjustments for Renal Function on Day 2.



Normal renal function is defined as a creatinine clearance of 81-150 mL/min/1.73m^2 estimated by the bedside Schwartz equation in pediatric patients and the BSA-normalized Cockcroft-Gault equation in adult patients. The black dashed lines represent the 25th and 75th percentile of AUC in adult patients with normal renal function and is used as an efficacy reference. The red dashed line represents the 75th percentile of AUC in adult patients with mild

renal impairment (51-80 mL/min/1.73m^2). The red line is used as a safety reference because patients with mild renal impairment experience a higher exposure of CAZ and AVI, but both agents are still considered safe without a dose adjustment. Simulated patients 18-20 years are used as a representative of adult exposure, because no further change in exposure is expected in adults due to age after renal function is accounted for.

Figure 3. Avibactam AUC in Simulated Patients with cIAI with Varying Renal Function Administered the Proposed Dose of Avibactam with and without Dose Adjustments for Renal Function on Day 2.



Normal renal function is defined as a creatinine clearance of 81-150 mL/min/1.73m^2 estimated by the bedside Schwartz equation in pediatric patients and the BSA-normalized Cockcroft-Gault equation in adult patients. The black dashed lines represent the 25th and 75th percentile of AUC in adult patients with normal renal function and is used as an efficacy reference. The red dashed line represents the 75th percentile of AUC in adult patients with mild renal impairment (51-80 mL/min/1.73m^2). The red line is used as a safety reference because patients with mild renal impairment experience a higher exposure of CAZ and AVI, but both agents are still considered safe without any additional dose adjustments. Simulated patients 18-20 years are used as a representative of adult exposure, because no further change in exposure is expected in adults due to age after renal function is accounted for.

Table 10 denotes the fold change in AUC relative to adult patients with normal renal function.

Table 10. Fold Change in AUC of CAZ and AVI in Simulated Patients with Varying Ages and Renal Function with and without Dose Adjustments for Renal Function Relative to the AUC of CAZ and AVI in Simulated Adult Patients with Normal Renal Function.

Age (yr)	Presence of Dose Adjustment	Normalized Creatinine Clearance (mL/min/1.73m^2)											
		0-5	6-15	16-30	31-50	51-80	81-150	0-5	6-15	16-30	31-50	51-80	81-150
		Fold Change* in Ceftazidime AUC						Fold Change* in Avibactam AUC					
2-6	Yes	1.0	1.1	1.0	1.2	-	-	1.2	1.3	1.2	1.5	-	-
	No	15.3	7.5	4.1	2.3	1.4	0.9	16.9	8.8	5.1	3.0	1.9	1.4
6-12	Yes	1.1	1.2	1.2	1.3	-	-	1.3	1.4	1.5	1.7	-	-
	No	16.4	9.1	4.3	2.7	1.7	1.1	18.9	10.7	5.5	3.5	2.2	1.6
12-18	Yes	0.8	1.1	1.1	1.2	-	-	0.8	1.2	1.3	1.5	-	-
	No	12.9	8.4	4.4	2.7	1.7	1.1	15.7	9.7	5.1	3.5	2.2	1.5
18-20	Yes	0.8	0.9	1.1	1.3	-	-	0.7	0.8	0.9	1.1	-	-
	No	14.8	7.7	4.1	2.5	**1.6**	**1.0**	14.7	6.7	3.6	2.1	**1.4**	**1.0**

*Fold change in AUC relative to adult (18-20 years) patients with normal renal function (eCrCl 81-150 mL/min/1.73m^2). For each category of age and creatinine clearance ranges, the adult (18-20 years) fold changes in patients with eCrCl range 81-150 mL/min/1.73m^2 and 51-80 mL/min/1.73m^2 (bolded and highlighted in yellow) are used as references for efficacy and safety, respectively. No dose adjustment is recommended for patients with eCrCl 51-150 mL/min/1.73m^2, and thus no values are shown in the corresponding cells.

From an efficacy perspective, all proposed doses provide CAZ and AVI AUCs similar to or greater than the efficacy reference (the AUCs in adult patients with eCrCl in the 81-150 mL/min/1.73m^2 range).

From a safety perspective, dose adjustments appear to be needed in patients with eCrCl less than 51 mL/min/1.73m^2. Administering the dose without an adjustment for renal function in these patients leads to ≥2-fold and ≥3-fold higher AUCs of CAZ and AVI, respectively, than the safety reference (the AUCs in adult patients with eCrCl in the 51-80 mL/min/1.73m^2 range).

Dose adjustments do not appear to be needed in patients with eCrCl in the 51-80 mL/min/1.73m^2 range. Some patients in this cohort administered the proposed dose of CAZ-AVI will have CAZ and AVI AUCs higher (<2-fold) than the safety reference. However, there were no major safety signals associated with CAZ and AVI in the pediatric patients with eCrCl 51-80 mL/min/1.73m^2.

It appears that the Applicant did not recommend dose adjustments in pediatric patients with eCrCl less than 31 mL/min/1.73m^2 because no patients in that eCrCl range were enrolled in the trial (see Table 9). However, PK data are limited in all pediatric patient subpopulations with renal impairment, and the population PK analysis is largely based on extrapolation of the effect of creatinine clearance on exposure in adult patients to pediatric patients. Thus, it is acceptable to provide dose adjustments in pediatric patients with values of eCrCl that were not included in the trial (i.e., <31 mL/min/1.73m^2).

Pediatric Patients <2 years

There is insufficient information to recommend a dose adjustment for renal impairment in pediatric patients <2 years. In fact, the submitted PK model is not developed to evaluate the effect of renal impairment in pediatric patients <2 years (see below). The Applicant did not propose any dose adjustments in this patient population. For patients 3 months-2 years, the Applicant recommended that the normal dose (i.e. the proposed dose in pediatric patients with eCrCl >80 mL/min/1.73m^2: 50-12.5 mg/kg q8h CAZ-AVI in patients 6 months-2 years and 40-10 mg/kg q8h CAZ-AVI in patients 3-6 months) be used in patients with eCrCl greater than 50 mL/min/1.73m^2. However, for patients 3-6 m, the Applicant does not provide a reference eCrCl range for when the normal dose should be used.

In the original efficacy supplement, the population PK model developed by the Applicant could not be used to evaluate the effect of renal impairment in pediatric patients <2 years due to the confounding factors introduced by renal function maturation. The Applicant used the Rhodin equation to describe renal function maturation.[2] However, this equation uses post-menstrual age (PMA) as a covariate instead of eCrCl. Thus, the model alone cannot account for changes in eCrCl, as a marker of renal function, in pediatric patients <2 years. Instead, the model assumes that PMA accounts for all changes in exposures of CAZ and AVI in patients <2 years but does not provide an option for reduced renal function beyond what was present in patients enrolled in the pediatric trials. This approach is generally acceptable, but it can only be used to simulate exposure of CAZ and AVI for patients in the eCrCl range included in the pediatric trials.

Based on the Applicant's and this reviewer's analysis, a PK model using the Rhodin equation alone (to describe the effect of age-related renal maturation on drug clearance) resulted in a better model fit than PK models using the bedside Schwartz equation (to describe the effect of eCrCl on drug clearance), either alone or in combination with the Rhodin equation, in pediatric patients <2 years. Each approach to describing drug clearance was evaluated by changing the estimating versions of the model with the corresponding covariate relationship on clearance. The model fit was evaluated by comparing goodness of fit, parameter precision, and objective function value. However, this observation may be confounded due to a lack of wide variation of eCrCl in the dataset.

Although in disagreement with the modeling results, it is physiologically plausible that both eCrCl and PMA affect drug clearance in pediatric patients <2 years. The model may not be able to identify the dual covariate relationship because the data are not robust enough to be statistically meaningful in pediatric patients <2 years. Thus, it may be reasonable to attempt to predict the effect of maturation and renal impairment on the exposure of CAZ and AVI in patients <2 years based on the assumption that both covariate relationships are independently

[2] Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76.

significant. In order to further explore this potential, an information request to attempt to qualify the relationship was sent to the Applicant.

In response to the Agency's information request, the Applicant attempted to predict doses in pediatric patients <2 years with renal impairment. They assumed that renal impairment in pediatric patients <2 years produces proportional changes in drug clearance as identified in adults and pediatric patients >2 years with different references for "normal" drug clearance, which is defined by the Rhodin equation for maturation. Using this approach, the Applicant simulated exposures in pediatric patients <2 years with renal impairment as shown in Table 11.

Table 11. Simulation of Exposure of CAZ and AVI in Adults and Pediatric Patients <2 years with cIAI with Varying Renal Function.

Age (years)	Renal Function	Presence of Dose Adjustment	CAZ AUC (mg*hr/L)	Fold Change* in CAZ AUC	AVI AUC (mg*hr/L)	Fold Change* in AVI AUC
0.25-0.5	Mild	No	982	1.6	172	1.6
0.25-0.5	Moderate	No	1594	2.6	276	2.6
0.25-0.5	Moderate	Yes	797	1.3	138	1.3
0.5-1	Mild	No	1020	1.7	187	1.7
0.5-1	Moderate	No	1650	2.7	302	2.8
0.5-1	Moderate	Yes	825	1.4	151	1.4
1-2	Mild	No	912	1.5	176	1.6
1-2	Moderate	No	1504	2.5	288	2.7
1-2	Moderate	Yes	752	1.2	144	1.3
Adults	**Normal**	No	**602**	**1.0**	**107**	**1.0**
Adults	Mild	No	**917**	**1.5**	**148**	**1.4**

*Fold Change in AUC is relative to adults with normal renal function. AUC is presented as the geometric mean. The dose adjustment in patients with moderate renal impairment is equal to halving the dose administered to patients with normal renal function. In children <2 years, the normal, mild, and moderate renal function categories are relative to age maturation based on the Rhodin function. The values of AUC and fold change of CAZ and AVI in adult patients with normal renal function and mild renal impairment (bolded and highlighted in yellow) are used as references for efficacy and safety, respectively.

All the doses in pediatric patients <2 years with and without renal impairment produce values of AUC that are higher than the efficacy reference, which indicates that the doses are likely effective. From a safety perspective, administering the normal dose without an adjustment for

renal function in pediatric patients <2 years with moderate renal impairment results in values of CAZ and AVI AUC over 1.7-2-fold higher than the safety reference (adult patients with mild renal impairment), suggesting the necessity of dose adjustments in patients with moderate renal impairment <2 years. Administering the normal dose without an adjustment for renal function in pediatric patients <2 years with mild renal impairment results in values of CAZ and AVI AUC that are under or reasonably similar to the safety reference.

There are several limitations to this method. Renal impairment categories were not defined according to eCrCl by the Applicant due to shift in the boundaries of the renal impairment categories with maturation. In order to define the renal impairment categories, different ranges of eCrCl would need to be listed by PMA on a weekly basis, particularly in patients under 6 months who are undergoing the fastest maturation. The need for a complex table in the labeling may make this strategy for dose adjustments difficult to apply clinically. There is currently no data available supporting the use of both the bedside Schwartz and Rhodin equations together as they were both designed to be used individually (see section 15.4 for more detail).

Taken together, there is insufficient information to recommend dose adjustments for renal impairment in patients <2 years due to the complexity of renal maturation. Administering the same dose to patients <2 years regardless of renal function may result in supratherapeutic exposure in patients with renal impairment. However, the optimal strategy to adjust the dose in this patient population remains to be determined.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Trials

The clinical safety and efficacy data were based on one pediatric trial in patients with complicated intra-abdominal infections (Study D4280C00015) and one pediatric trial in patients with complicated urinary tract infections (Study D4280C00016). The table below summarizes these studies. Both trials were randomized, single-blind, active-controlled, and descriptively analyzed.

Table 12: Completed Phase 2 pediatric PREA studies

Study number (clinicaltrials.gov identifier)	Indication	Age and cohort	Type of study	Design
Study D4280C00015 (NCT02475733)	Complicated intra-abdominal infections (cIAI)	Cohort 1: ≥ 12 to < 18 years Cohort 2: ≥ 6 to < 12 years Cohort 3: ≥ 2 to < 6 years Cohort 4: Full-term infants aged ≥ 3 months to < 2 years (split into 2 groups: ≥ 3 months to < 1 year, and ≥ 1 to < 2 years)	Phase 2, multicenter, randomized, single-blind safety, tolerability, and descriptive efficacy study in pediatric patients aged 3 months to < 18 years with cIAI	Primary endpoints: safety, and tolerability. Sample size in completed study: 61 CAZ-AVI; 22 meropenem First subject first visit: 01 August 2015; Last subject last visit: 01 June 2017.
Study D4280C00016 (NCT02497781)	Complicated urinary tract infections (cUTI)		Phase 2, multicenter, randomized, single-blind safety, tolerability, and descriptive efficacy study in pediatric	Primary endpoints: safety, and tolerability. Sample size in completed study: 67 CAZ-AVI;

			patients aged 3 months to <18 years with cUTI	28 cefepime First subject first visit: 24 September 2015; Last subject last visit: 15 September 2017

Source: Summary of Clinical Safety, Table 1.1.6.2-1.

7.1.2. Review Strategy

For the indications of cIAI and cUTI, efficacy in pediatrics is traditionally extrapolated from adults. Therefore, the pediatric studies were designed with relatively small sample size and primary objectives of evaluating safety and tolerability. Efficacy results were assessed descriptively.

Data Sources

Data sources reviewed included patient-level datasets, study reports, protocols, statistical analysis plans, case and report forms.

The SDTM and ADaM datasets are available at the following location in the Agency's Electronic Document Room: \\CDSESUB1\evsprod\NDA206494\0084\m5\datasets

Data and Analysis Quality

The quality of submitted data was sufficient for review purposes. It was possible to reproduce the applicant's main analysis results without complex manipulations. The protocols and statistical analysis plans were sufficiently precise and comprehensive, and the applicant's reported analyses were consistent with planned analyses.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Pediatric cIAI Study D4280C00015

Trial Design and Endpoints

The primary objective of Study D4280C00015 was to evaluate the safety and tolerability of ceftazidime-avibactam plus metronidazole given at the selected dose regimen versus meropenem in pediatric patients aged ≥3 months to <18 years with cIAI. Secondary objectives were to descriptively evaluate efficacy and to evaluate the pharmacokinetics of ceftazidime-avibactam.

Patients were randomized to ceftazidime-avibactam plus metronidazole versus meropenem in a 3:1 ratio. Metronidazole was added to the regimen for the AVYCAZ treatment group to provide coverage for anaerobic organisms, which was extrapolated from adult cIAI studies. Pediatric dosing of metronidazole 10mg/kg every 8 hours is used in clinical practice and is supported by the pediatric literature, including the 2010 IDSA guidelines on treatment of cIAI in adult and pediatric patients. Metronidazole was not expected to impact efficacy analysis of Gram-negative disease because metronidazole does not have sufficient activity against the Gram-negative pathogens commonly causing these infections. Metronidazole was not given in the control group because meropenem has activity against the relevant anaerobic pathogens. Patients received intravenous treatment for a minimum of 72 hours before having the option to switch to an oral therapy on Day 4.

Ceftazidime-avibactam doses were based on the age and weight of the patient with adjustments for renal function, as described in the following table.

Table 13: Ceftazidime-avibactam Dose Regimens by Age, Weight, and Creatinine Clearance

Cohort	Age range	Body weight	Ceftazidime-avibactam dose by creatinine clearance	
			≥50 mL/min	≥30 to <50 mL/min
1	12 to <18 years	≥40 kg	2000 mg CAZ/ 500 mg AVI	1000 mg CAZ/ 250 mg AVI
1	12 to <18 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
2	6 to <12 years	≥40 kg	2000 mg CAZ/ 500 mg AVI	1000 mg CAZ/ 250 mg AVI
2	6 to <12 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
3	2 to <6 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4a	1 to <2 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	6 months to <1 year	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	3 to <6 months	All	40 mg/kg CAZ 10 mg/kg AVI	20 mg/kg CAZ/ 5 mg/kg AVI

Source: Study D4280C00015 Clinical Study Report, Table 3.
Notes: Ceftazidime-avibactam was administered as a 50 to 100 mL infusion (dependent on dose) over 2 hours every 8 hours (±30 minutes). CAZ = ceftazidime; AVI = avibactam.

Ceftazidime-avibactam was infused over 2 hours, followed by metronidazole infused over 20 to 30 minutes. Meropenem 20 mg/kg was infused over approximately 15 to 30 minutes (up to 1 hour), or infusion duration as per local guidelines. For patients weighing over 50 kg, the maximum dose of meropenem was not to exceed 1 g every 8 hours.

The optional oral switch on or after Day 4 was at the investigator's discretion, if the patient had good or sufficient clinical response and the patient was tolerating oral fluids or foods. Oral amoxicillin/clavulanic acid, oral ciprofloxacin, or pathogen-based therapy (in discussion with the Medical Monitor) were permitted for the oral switch and were administered per local standards of care. The total duration of therapy (intravenous and oral) was to be between 7 and 15 days. Patients could remain on intravenous study treatment for the entire period.

Open-label vancomycin, linezolid, or daptomycin could also be used in either study arm to provide coverage for *Enterococcus* species or methicillin-resistant *Staphylococcus aureus*. These

drugs generally lack activity against Gram-negative pathogens, so were not expected to impact efficacy analysis, and were only used by 3 patients in the trial.

This study was observer-blinded. Each study site was to have a site-specific blinding plan and have at least 1 blinded investigator, referred to as the Blinded Observer. The Blinded Observer was to see the patient during times when the study drug was not being administered, and when possible was to complete all clinical assessments and perform causality assessments for adverse events and serious adverse events.

Post-baseline study visits were defined at the following times to assess safety, efficacy, and pharmacokinetics:

- An end of intravenous treatment (EOIV) visit. Assessments were to be performed by a Blinded Observer within 24 hours after completing the last infusion of study drug, or at the time of premature discontinuation of study drug or withdrawal from the study. Assessments were to occur before starting oral switch therapy.
- An end of treatment (EOT) visit. Assessments were to be performed in person within 48 hours after the last dose of oral switch therapy, or at the time of premature discontinuation of study drug or withdrawal from the study (if on oral switch therapy). For patients who did not switch to oral therapy, the EOIV and EOT visits coincided.
- A test of cure (TOC) visit. Assessments were to be performed in person 8 to 15 days after the last dose of any study drug (IV or oral).
- A late follow-up (LFU) visit. Assessments were to be performed 20 to 35 days after the last dose of study drug (IV or oral). Assessments were to be conducted by telephone for any patient who had not experienced clinical relapse, did not have ongoing adverse events or serious adverse events at the TOC visit or afterwards. If symptoms of relapse or new adverse events were noted, or at the discretion of the Blinded Observer or Investigator, an in-person visit was to be scheduled immediately.

The planned sample size in the trial was 80 subjects. Patients were to be allocated to 1 of 4 cohorts based on age, and randomization was to be stratified by cohort as follows:

- Cohort 1: At least 15:5 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 15:5 evaluable patients aged from 6 years to <12 years;
- Cohort 3: No required minimum number of evaluable patients aged from 2 years to <6 years;
- Cohort 4: No required minimum number of evaluable patients aged from 3 months to <2 years, comprising Cohorts 4a and 4b as follows:
    - Cohort 4a: Patients aged from 1 year to <2 years
    - Cohort 4b: Patients aged from 3 months to <1 year.

Patients, the patient's parent(s), or legally acceptable representative(s) could discontinue use of study drug or withdraw from the study. Follow-up assessments were to be made for patients who discontinued therapy, and alternative therapies could be given at the Investigator's

discretion. Patients were to be withdrawn from study therapy if their creatinine clearance dropped below 30 mL/min.

The primary outcome variables for assessing safety were as follows:

- Adverse events and serious adverse events
- Cephalosporin class effects and additional adverse events of special interest
- Vital signs (pulse, blood pressure, respiratory rate, temperature)
- Physical examination results
- Laboratory parameters
- Creatinine clearance

As previously noted, efficacy evaluations were a secondary purpose of the study. The efficacy outcome measures were defined as follows:

- Clinical response at the End of 72 hours treatment, EOIV, EOT, and TOC;
- Microbiological response at EOIV, EOT, TOC, and LFU;
- Clinical relapse at LFU;
- Emergent infections.

The subsequent tables define clinical and microbiological outcome assessments in greater detail for various study visits.

Table 14: Clinical Outcome Assessments at the End of Intravenous Treatment

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Improvement	Patients who switch to oral therapy and meet all of the following criteria at EOIV: • Afebrile (temperature ≤38.0°C) for at least 24 hours • Absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none
Clinical Failure[a]	Patients who meet any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cIAI that requires alternative non-study antimicrobial therapy; • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cIAI; • Death in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00015 Clinical Study Report, Table 6.
Notes: [a] A clinical failure at EOIV was carried forward to EOT and TOC.
AE = adverse event; CRP = C-reactive protein; WBC = white blood cell.

Table 15: Clinical Outcome Assessments at the Test of Cure

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cIAI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Failure	Patients who meet either of the following criteria: • Incomplete resolution or worsening of cIAI signs or symptoms or development of new signs or symptoms requiring alternative non-study antimicrobial therapy; • Death in which cIAI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cIAI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00015 Clinical Study Report, Table 8.

Table 16: Microbiological Outcome Definitions

Outcome	Definition
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Presumed eradication	Source specimen was not available to culture, and the patient was assessed as a clinical cure or sustained clinical cure or (for EOIV only) clinical improvement
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Persistence with increasing MIC[a]	Source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥4-fold larger than that observed for the baseline pathogen
Presumed persistence	Source specimen was not available to culture and the patient was assessed as a clinical failure or clinical relapse
Indeterminate	Source specimen was not available to culture and the patient's clinical outcome was assessed as indeterminate

Source: Study D4280C00015 Clinical Study Report, Table 10.
Notes: [a] Persistence with increasing MIC is a subset of the persistence outcome.
EOIV = end of intravenous treatment; MIC = minimum inhibitory concentration.

Key Inclusion and Exclusion Criteria

The following inclusion criteria were required for enrollment:

1. Patients must have been ≥3 calendar months to <18 years of age. Patients aged ≥3 calendar months to <1 year must have been born at term (gestational age ≥37 weeks).
2. Written informed consent obtained from parent(s) or other legally acceptable representative(s), and informed assent obtained from patient (if age appropriate according to local regulations).
3. For females who had reached menarche, or had reached Tanner stage 3 development, the patient was authorized to participate in this clinical study if contraceptive criteria

(specified in the protocol) were met.

4. Must, based on the judgment of the Investigator, have required hospitalization initially and antibacterial therapy for 7 to 15 days in addition to the surgical intervention for the treatment of the current cIAI.
5. Required surgical intervention (e.g., laparotomy, laparoscopic surgery or percutaneous drainage) to manage the cIAI.
6. Must have had clinical evidence of cIAI as follows:
    a. Pre-operative enrollment inclusion:
        i. Required surgical intervention that was expected to be completed within 24 hours of enrollment: laparotomy, laparoscopy, or percutaneous drainage.
        ii. Evidence of a systemic inflammatory response. At least 1 of: fever (defined as oral temperature >38.5°C, or equivalent to method used) or hypothermia (with a core body or rectal temperature <35°C, or equivalent to method used); elevated white blood cells (WBC) (>15000 cells/mm^3); C-reactive protein (CRP) levels (>10 mg/L).
        iii. Physical findings consistent with intra-abdominal infection, such as: abdominal pain and/or tenderness; localized or diffuse abdominal wall rigidity; abdominal mass.
        iv. Intention to send specimens from the surgical intervention for culture.
        v. (Optional) Supportive radiologic findings of intra-abdominal infection, such as perforated intraperitoneal abscess detected on computed tomography (CT) scan, or magnetic resonance imaging (MRI), or ultrasound .
    b. Intra-operative/postoperative enrollment inclusion (in cases of postoperative enrollment, must be within 24 hours after the time of incision):
    Visual confirmation of intra-abdominal infection associated with peritonitis at laparotomy, laparoscopy or percutaneous drainage (to be confirmed pending feasibility); must have 1 of these diagnoses: appendiceal perforation or peri-appendiceal abscess; cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall; acute gastric or duodenal perforations, only if operated on >24 hours after the singular perforation occurs; traumatic perforation of the intestines, only if operated on >12 hours after perforation occurs; secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites).

Subjects were ineligible for the study if any of the following exclusion criteria were met:

1. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study site).
2. Previous enrollment or randomization in the present study.
3. Participation in another clinical study with an IP during the last 30 days before the first dose of IV study drug or previous participation in the current study or in another study of CAZ-AVI (in which an active agent was received).

4. History of hypersensitivity reactions to carbapenems, cephalosporins, penicillin, other β-lactam antibiotics, metronidazole, or to nitroimidazole derivatives.
5. Concurrent infection that may have interfered with the evaluation of response to the study antibiotics at the time of randomization.
6. Patient needed effective concomitant systemic antibacterials (oral, IV, or intramuscular) in addition to those designated in the 2 study drugs (CAZ-AVI plus metronidazole group or meropenem group).
7. Receipt of non-study systemic antibacterial drug therapy for cIAI, for a continuous duration of more than 24 hours during the 72 hours preceding the first dose of IV drug, except in the case of proven pathogen resistance to the administered antibacterial drug and/or worsening of the clinical condition. More than 2 consecutive doses were not permitted if the individual doses are expected to give >12 hours cover (i.e., giving a total cover of >24 hours). For patients enrolled after a surgical procedure, only 1 dose of non-study antibiotics was permitted postoperatively.
8. Patient was considered unlikely to survive the 6 to 8 week study period.
9. Patient was unlikely to respond to 7 to 15 days of treatment with antibiotics.
10. Patient was receiving hemodialysis or peritoneal dialysis.
11. Diagnosis of abdominal wall abscess confined to musculature of the abdominal wall or ischemic bowel disease without perforation, traumatic bowel perforation requiring surgery within 12 hours of perforation, or perforation of gastroduodenal ulcers requiring surgery within 24 hours of perforation (these are considered situations of peritoneal soiling before the infection has become established).
12. Simple (uncomplicated), non-perforated appendicitis or gangrenous appendicitis without rupture into the peritoneal cavity identified during a surgical procedure OR presence of primary peritonitis (i.e., spontaneous bacterial peritonitis) or peritonitis associated with cirrhosis or chronic ascites.
13. At the time of randomization, the patient was known to have had a cIAI caused by pathogens resistant to the study antimicrobials planned to be used in the study.
14. Presence of any of the following clinically significant laboratory abnormalities, unless these values were acute and directly related to the infectious process being treated:
    a. Hematocrit <25% or hemoglobin <8 g/dL (<80 g/L, <4.9 mmol/L);
    b. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x the age-specific upper limit of normal (ULN), or total bilirubin >2 x ULN (except known Gilbert's disease).
15. Creatinine clearance (CrCl) <30 mL/min/1.73 m^2 calculated using the child's measured height (length) and serum creatinine within the updated "bedside" Schwartz formula:
    CrCl (mL/min/1.73 m^2) = 0.413 x height (length) (cm)/serum creatinine (mg/dL).
16. History of seizures excluding well-documented febrile seizure of childhood.
17. Any situation or condition that would have made the patient, in the opinion of the Investigator, unsuitable for the study (e.g., would have placed a patient at risk or compromised the quality of the data) or may have interfered with optimal participation in the study.
18. If female, currently pregnant or breast feeding.

Statistical Analysis Plan

Both safety and efficacy variables were analyzed using descriptive summaries, and there was no hypothesis testing or corresponding adjustments for multiple comparisons. No interim analyses were performed for efficacy, but a data safety monitoring board assessed safety results.

The statistical analysis plan defined the following analysis sets:

- Safety Analysis Set: All randomized patients who received any amount of IV study therapy (i.e., ceftazidime-avibactam plus metronidazole or meropenem). For the safety analysis set, patients were included in all outputs according to the study treatment they actually received.
- Safety Evaluable Analysis Set: A subset of the patients in the safety analysis set who received at least 9 doses of study treatment. Each subject's dosing profile was received by unblinded medical personnel to confirm evaluability.
- PK Analysis Set: A subset of the patients in the safety analysis set who had at least 1 ceftazidime and/or avibactam plasma measurement available.
- Intent-to-Treat (ITT) Analysis Set: All patients who were assigned a randomized treatment.
- Microbiological Intent-to-Treat (micro-ITT) Analysis Set: All randomized patients who had a baseline pathogen known to cause cIAI.
- Clinically Evaluable (CE) Analysis Set: The CE analysis set was defined separately at the end of 72 hours of study treatment, and at each of the EOIV, EOT, TOC, and LFU visits. The CE analysis set included all randomized patients who received any amount of IV study drug and had a diagnosis of cIAI, and patients must have also met the following specific conditions:
    - Received at least 48 hours of IV study drug, unless deemed a clinical failure based on a treatment-limiting adverse event;
    - Received at least 72 hours of IV study drug in order to be considered an evaluable clinical cure;
    - Had a clinical response other than indeterminate at the associated study visit;
    - Had no important protocol deviations that would affect assessment of efficacy based on a blinded Evaluability and Clinical/Microbiological Assessment (ECMA) review committee.
    - Did not receive concomitant antibiotics which would impact assessment of efficacy based on ECMA review.
- Microbiologically Evaluable (ME) Analysis Set: The ME analysis set was defined separately at the end of 72 hours of study treatment, and at each of the EOIV, EOT, TOC, and LFU visits. It similar to the CE analysis set but required a microbiological response other than indeterminate rather than a clinical response other than indeterminate. Patients also were to have at least 1 typical IAI bacterial pathogen isolated from an adequate baseline microbiological specimen that was susceptible to both ceftazidime-avibactam and meropenem. The statistical analysis plan defined specific criteria for determination of susceptibility.

The safety analysis set was used by the applicant for all safety summaries, unless otherwise specified. The ITT analysis set was defined for efficacy analysis, but in this trial happened to exactly correspond with the safety analysis set.

Due to the primary objectives of assessing safety and tolerability, the study design did not necessarily completely adhere to recommendations in the FDA guidance document for cIAI trials in adults (available at https://www.fda.gov/downloads/drugs/guidances/ucm321390.pdf). The guidance recommendations were meant to optimize efficacy assessments of noninferiority. One difference is the timing of the TOC cure endpoint, which the guidance recommends at approximately 28 days after randomization in the guidance rather than the post-therapy window used in this trial. The guidance also recommends that the primary efficacy analysis be conducted in the microbiological intent-to-treat population rather than the ITT analysis set. Further, the definition of clinical cure given in the previous subsection required resolution of signs and symptoms to the extent that further antimicrobial therapy was not warranted, while the guidance instead defined clinical failure programmatically as death, surgical site wound infection, unplanned surgical procedures or drainage procedures for cIAI, or initiation of non-trial antibacterial therapy for worsening of cIAI.

Protocol Amendments

The applicant summarizes the protocol amendments as follows: *"There were two protocol amendments following the original approval on 20 January 2015. Amendment 1 was approved on 22 September 2015 and this modification provided additional doses for Cohort 4 and dose adjustments for patients with renal impairment. Amendment 2 was approved 07 March 2017 with endorsement from the European Medicines Agency Paediatric Committee (PDCO) to increase the maximum percentage of patients enrolled with complicated appendicitis from 80% to 90%, remove the requirement for a minimum number of evaluable patients to be enrolled in Cohorts 3 and 4, and remove specific exclusionary criteria related to immunocompromised patients. Amendment 2 also included the addition of two efficacy analysis sets (intent-to-treat [ITT] and microbiological intent-to-treat [micro-ITT]) per agreement with the Food and Drug administration (FDA)."*

7.2.2. Study Results

Compliance with Good Clinical Practices

The applicant states that *"This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents."*

Financial Disclosure

There were no significant financial conflicts of interest identified among the study site

investigators. Please see section 15.2 of this review.

Patient Disposition

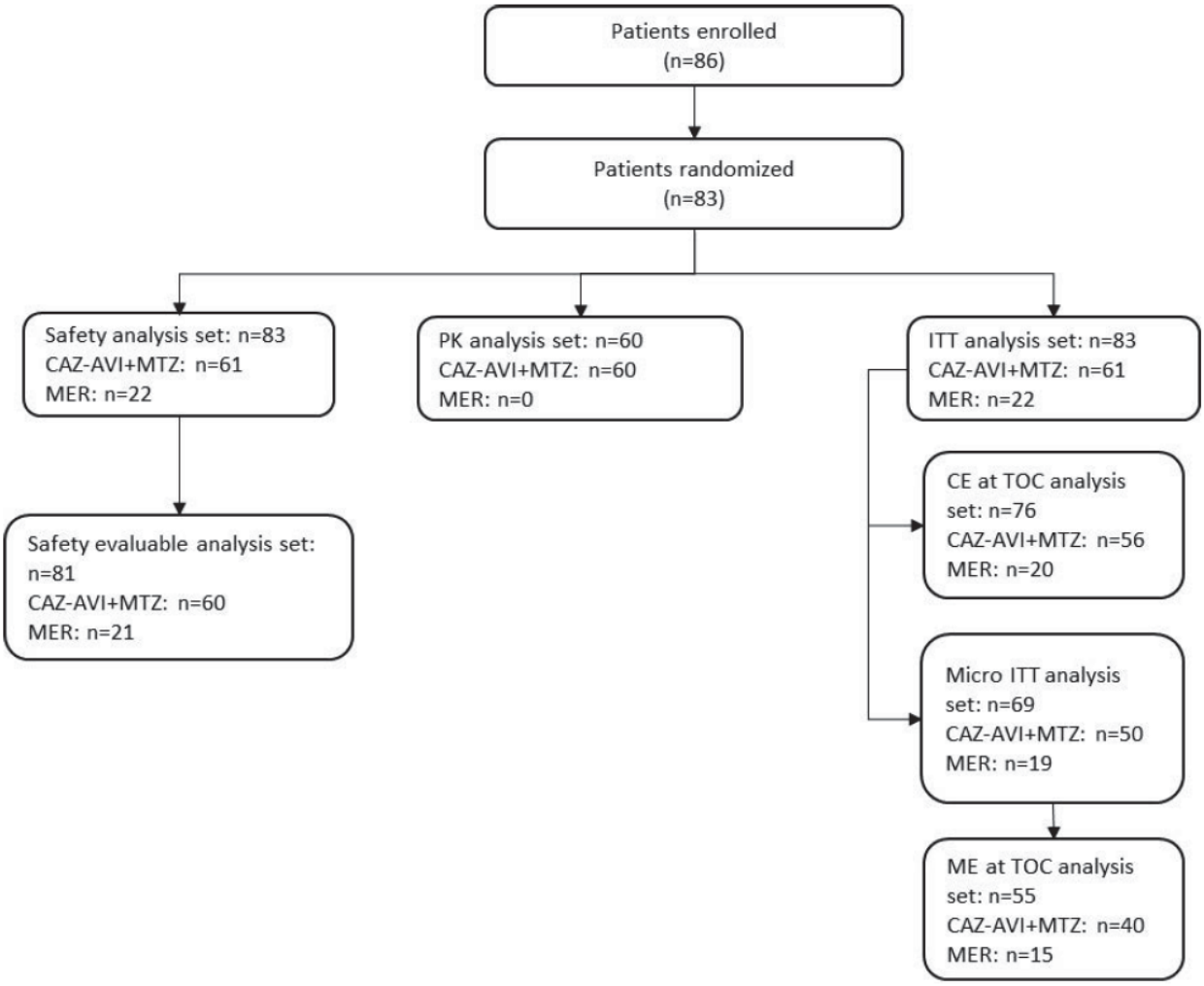
The table below displays patient disposition in the trial. There were 83 randomized patients, including 61 in the ceftazidime-avibactam plus metronidazole group and 22 in the meropenem control group. All but 2 of these patients completed the study. Most enrollment was in the older age cohorts, with only a single patient enrolled in Cohort 4 with age <2 years. The subsequent figure also displays membership in various analysis sets. All randomized patients were included in the ITT and safety analysis sets (which exactly coincided), approximately 92% of randomized patients were considered clinically evaluable at the TOC visit, and approximately 83% of patients were in the micro-ITT analysis set with a baseline pathogen.

Table 17: Patient Disposition

	Number (%) of patients Cohort/Treatment Group														
	Cohort 1			Cohort 2			Cohort 3			Cohort 4			All Cohorts		
	CAZ-AVI + MTZ (N = 22)	MER (N = 8)	Total (N = 30)	CAZ-AVI + MTZ (N = 33)	MER (N = 10)	Total (N = 45)	CAZ-AVI + MTZ (N = 6)	MER (N = 3)	Total (N = 10)	CAZ-AVI + MTZ (N = 0)	MER (N = 1)	Total (N = 1)	CAZ-AVI + MTZ (N = 61)	MER (N = 22)	Total (N = 86)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients randomised	22 (100)	8 (100)	30 (100)	33 (100)	10 (100)	43 (95.6)	6 (100)	3 (100)	9 (90.0)	0	1 (100)	1 (100)	61 (100)	22 (100)	83 (96.5)
Patients who received IV study treatment	22 (100)	8 (100)	30 (100)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	61 (100)	22 (100)	83 (100)
Patients who completed the study up to the TOC visit	20 (90.9)	8 (100)	28 (93.3)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	59 (96.7)	22 (100)	81 (97.6)
Patients who completed the study up to the LFU visit	19 (86.4)	8 (100)	27 (90.0)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	58 (95.1)	22 (100)	80 (96.4)
Patients who completed IV study treatment	20 (90.9)	7 (87.5)	27 (90.0)	32 (97.0)	10 (100)	42 (97.7)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	58 (95.1)	21 (95.5)	79 (95.2)
Patients who discontinued IV study treatment	2 (9.1)	1 (12.5)	3 (10.0)	1 (3.0)	0	1 (2.3)	0	0	0	0	0	0	3 (4.9)	1 (4.5)	4 (4.8)
Lack of therapeutic response	1 (4.5)	0	1 (3.3)	0	0	0	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)
Condition under investigation improved/patient recovered	0	1 (12.5)	1 (3.3)	0	0	0	0	0	0	0	0	0	0	1 (4.5)	1 (1.2)
Other	0	0	0	1 (3.0)	0	1 (2.3)	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)
Patients who completed study	20 (90.9)	8 (100)	28 (93.3)	33 (100)	10 (100)	43 (100)	6 (100)	3 (100)	9 (100)	0	1 (100)	1 (100)	59 (96.7)	22 (100)	81 (97.6)
Patients prematurely withdrawn from study	2 (9.1)	0	2 (6.7)	0	0	0	0	0	0	0	0	0	2 (3.3)	0	2 (2.4)
Parent/Guardian decision	1 (4.5)	0	1 (3.3)	0	0	0	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)
Investigator determination	1 (4.5)	0	1 (3.3)	0	0	0	0	0	0	0	0	0	1 (1.6)	0	1 (1.2)

Source: Study D4280C00015 Clinical Study Report, Table 15.
Notes: Cohort 1: ≥12 years to <18 years of age; Cohort 2: ≥6 years to <12 years of age; Cohort 3: ≥2 years to <6 years of age; Cohort 4: ≥3 months to <24 months of age; Percentages for the patients randomized and patients not randomized use all patients in the cohort as the denominator. Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the denominator. CAZ-AVI + MTZ = ceftazidime avibactam plus metronidazole; IV = intravenous; MER = meropenem; TOC = test of cure; LFU = late follow-up.

Figure 4: Flow Chart of Analysis Sets



Source: Study D4280C00015 Clinical Study Report, Figure 2.
Notes: CAZ-AVI + MTZ = ceftazidime-avibactam plus metronidazole; CE = clinically evaluable; ITT = intent-to-treat; ME = microbiologically evaluable; MER = meropenem; micro-ITT = microbiological intent-to-treat; PK = pharmacokinetic; TOC = test of cure.

Protocol Violations/Deviations

The table below shows protocol deviations in the safety analysis set that were classified by the applicant as important. Over half of patients had at least one such protocol deviation. The most common deviations were in the category "Assessment – safety." The applicant's Clinical Study Report states that most deviations within this category were related to assessments not being conducted per the study schedule.

Table 18: The Applicant's Summary of Important Protocol Deviations (Safety Analysis Set)

Important Protocol Deviation Category	CAZ-AVI + MTZ (N = 61) n (%)	MER (N = 22) n (%)	Total (N = 83) n (%)
Number of patients with at least one protocol deviation	35 (57.4)	10 (45.5)	45 (54.2)
Assessment - Safety	20 (32.8)	4 (18.2)	24 (28.9)
Visit Window	12 (19.7)	3 (13.6)	15 (18.1)
Study Drug	12 (19.7)	2 (9.1)	14 (16.9)
Informed Consent	6 (9.8)	0	6 (7.2)
Other	4 (6.6)	2 (9.1)	6 (7.2)
Lab/Endpoint Data	5 (8.2)	0	5 (6.0)
Overdose/Misuse	0	4 (18.2)	4 (4.8)
Exclusion Criteria	2 (3.3)	0	2 (2.4)
Prohibited Co-medication	2 (3.3)	0	2 (2.4)

Source: Study D4280C00015 Clinical Study Report, Table 16.
Notes: Important protocol deviations were defined and identified prior to database lock. Patients with multiple deviations in single category were counted once for each category. CAZ-AVI = MTZ = ceftazidime avibactam plus metronidazole; MER = meropenem.

Demographic Characteristics

The subsequent table displays demographic characteristics of the safety analysis set. As previously noted, most enrollment was in the older age cohorts. The trial included both males and females, most patients were White, and enrollment was predominately in Europe. Due to the small sample size, the treatment and control groups were not necessarily well balanced on demographic factors or other baseline characteristics. For instance, the meropenem group had a much larger proportion of females than the ceftazidime-avibactam plus metronidazole group.

Table 19: Demographic Characteristics (Safety Analysis Set)

	Ceftazidime-avibactam plus metronidazole (n = 61)	Meropenem (n = 22)
Age Cohort		
Cohort 1: 12 years to <18 years	22 (36.1%)	8 (36.4%)
Cohort 2: 6 years to <12 years	33 (54.1%)	10 (45.5%)
Cohort 3: 2 years to <6 years	6 (9.8%)	3 (13.6%)
Cohort 4a: 1 year to <2 years	0 (0.0%)	1 (4.5%)
Cohort 4b: 3 months to <1 year	0 (0.0%)	0 (0.0%)
Sex		
Female	17 (27.9%)	13 (59.1%)
Male	44 (72.1%)	9 (40.9%)
Race		
American Indian or Alaska native	1 (1.6%)	0 (0.0%)
Asian	7 (11.5%)	4 (18.2%)

Black or African American	0 (0.0%	0 (0.0%)
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	2 (9.1%)
White	53 (86.9%)	16 (72.7%)
Ethnicity		
Hispanic or Latino	12 (19.7%)	1 (4.5%)
Non-Hispanic or Latino	49 (80.3%)	21 (95.5%)
Country of Enrollment		
Czech Republic	7 (11.5%)	5 (22.7%)
Greece	2 (3.3%)	3 (13.6%)
Hungary	14 (23.0%)	1 (4.5%)
Poland	1 (1.6%)	0 (0.0%)
Romania	1 (1.6%)	1 (4.5%)
Russia	3 (4.9%)	0 (0.0%)
Turkey	6 (9.8%)	1 (4.5%)
Taiwan	6 (9.8%)	4 (18.2%)
Spain	14 (23.0%)	2 (9.1%)
United States	7 (11.5%)	5 (22.7%)

Source: Statistical reviewer and Study D4280C00015 Clinical Study Report, Table 14.1.2.1.1.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
The subsequent table shows additional baseline patient characteristics in the safety analysis set. All patients in the trial had estimated creatinine clearance ≥50 mL/min/1.73 m^2, over 90% of patients in both treatment groups had appendicitis at screening, and the diagnosis of cIAI was most commonly based on a diagnosis of appendiceal perforation or peri-appendiceal abscess.

Table 20: Patient Characteristics at Baseline (Safety Analysis Set)

	Ceftazidime-avibactam plus metronidazole (n = 61)	Meropenem (n = 22)
Height (cm)		
Mean (Standard Deviation)	145.8 (22.0)	141.3 (24.0)
Median	147.0	140.0
(Minimum, Maximum)	(102, 185)	(81, 173)
Body Mass Index (kg/m^2)		
Mean (Standard Deviation)	18.1 (3.4)	18.4 (4.4)
Median	17.6	17.4
(Minimum, Maximum)	(13, 26)	(12, 28)
Creatinine Clearance (mL/min/1.73 m^2)		
<30	0 (0.0%)	0 (0.0%)
≥30 to <50	0 (0.0%)	0 (0.0%)
≥50 to <80	9 (14.8%)	2 (9.1%)
≥80	51 (83.6%)	20 (90.9%)
Type of Procedure		
Laparoscopy	14 (23.0%)	9 (40.9%)
Laparotomy	8 (13.1%)	2 (9.1%)
Percutaneous Drainage	3 (4.9%)	2 (9.1%)
Appendectomy (not otherwise specified)	36 (59.0%)	9 (40.9%)
Appendicitis at Screening		
Yes	55 (90.2%)	20 (90.9%)
No	6 (9.8%)	2 (9.1%)
Diagnosis of intra-abdominal infection		
Appendiceal Perforation or Peri-Appendiceal Abscess	52 (85.2%)	20 (90.9%)
Secondary Peritonitis (But not Spontaneous Bacterial Peritonitis Associated with Cirrhosis and Chronic Ascites)	8 (13.1%)	1 (4.5%)

Traumatic Perforation of the Intestines (Only if operated on >12 Hours After Perforation Occurs)	1 (1.6%)	1 (4.5%)

Source: Study D4280C00015 Clinical Study Report, Table 21.

Notes: Body mass index was not calculated for children <24 months of age (Cohort 4). Height and body mass index responses were the last non-missing values obtained prior to first administration of study medication. Creatinine Clearance results were as recorded on the case report form using the Bedside Schwartz formula. Percentages were based on the total number of patients in the treatment group.

Over 80% of patients in each treatment group of the safety analysis set belonged to the micro-ITT analysis set, and thus had baseline pathogens identified from intra-abdominal or blood cultures. The table below shows baseline pathogens in the micro-ITT analysis set. The most common infecting pathogen was *E. coli*. Two patients in the ceftazidime-avibactam metronidazole group had *E. coli* isolates reported as non-susceptible to ceftazidime (without the beta-lactamase inhibitor, which restored susceptibility). No patients in the meropenem group were reported as having meropenem non-susceptible isolates.

Table 21: Baseline Pathogens in ≥2 Patients in either Treatment Group (Micro-ITT Analysis Set)

	Ceftazidime-avibactam (n = 50)	Meropenem (n = 19)
Enterobacteriaceae		
Escherichia coli	42 (84.0%)	13 (68.4%)
Klebsiella pneumoniae	2 (4.0%)	1 (5.3%)
Gram-negative other than Enterobacteriaceae	16 (32.0%)	10 (52.6%)
Pseudomonas aeruginosa	14 (28.0%)	9 (47.4%)
Gram-positive	26 (52.0%)	11 (57.9%)
Enterococcus avium	4 (8.0%)	1 (5.3%)
Enterococcus faecium	2 (4.0%)	0 (0.0%)
Streptococcus anginosus group	23 (46.0%)	10 (52.6%)
Anaerobes	24 (48.0%)	12 (63.2%)
Bacteroides caccae	3 (6.0%)	0 (0.0%)
Bacteroides fragilis	14 (28.0%)	7 (36.8%)
Bacteroides fragilis group	2 (4.0%)	2 (10.5%)
Bacteroides ovatus	2 (4.0%)	0 (0.0%)
Bacteroides thetaiotaomicron	3 (6.0%)	3 (15.8%)
Bacteroides vulgatus	2 (4.0%)	0 (0.0%)

Clostridium perfringens	0 (0.0%)	2 (10.5%)
Clostridium ramosum	2 (4.0%)	0 (0.0%)
Eggerthella lenta	2 (4.0%)	0 (0.0%)
Parabacteroides distasonis	2 (4.0%)	0 (0.0%)
Parvimonas micra	4 (8.0%)	5 (26.3%)
Prevotella buccae	2 (4.0%)	0 (0.0%)

Source: Study D4280C00015 Clinical Study Report, Table 22.
Notes: Pathogens included in this table were collected from intra-abdominal site and/or blood. A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Likewise, patients with multiple isolates within the same pathogen group were counted only once for that pathogen group.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The applicant states that "Treatment compliance over the entire treatment period was defined as the number of infusions over all doses received, divided by the number of infusions over all doses expected during the treatment period, then multiplied by 100." Mean compliance values were 100% (SD = 1.8) for ceftazidime-avibactam, 99.8% (SD = 2.3) for metronidazole, and 100.7% (SD = 1.5) for meropenem. Thus, treatment compliance appeared to be high in this trial.

Concomitant medications given as rescue medication were not an issue in interpreting safety or efficacy in this study, because as will be described below, there were very few clinical failures.

In each treatment group, only 1 patient was excluded from the CE and ME analysis sets (at the EOIV, EOT, and TOC visits) for being in receipt of concomitant medication for a reason other than clinical failure. However, the applicant reports that >86% of subjects in each treatment group received concomitant antibiotics, including >26% of subjects in each treatment group who received concomitant gentamycin. The applicant's explanation for this discrepancy is that "This apparent high proportion could be explained by the fact that since time of dose was not collected, systemic antibiotics taken during Day 1 of IV study medication administration are reported as both prior and concomitant medications." Concomitant therapies other than systemic antibiotics were used by almost all patients in the trial. The duration of therapy was relatively similar between the treatment groups. Approximately 69% of patients in both groups switched to oral therapy to complete the treatment course, and the median duration of IV and oral exposure was approximately 12 days in each treatment group.

Efficacy Results

The subsequent tables display results for favorable clinical and microbiological responses at various study visits and analysis populations. Favorable clinical response was defined as clinical cure, sustained clinical cure (at the LFU visit), or clinical improvement (at the end of 72 hour or EOIV visits). Both treatment groups generally had high rates of favorable clinical response, and both groups had clinical cure rates of >90% at the TOC visit in the ITT analysis set. Only 1 patient

was classified as having an indeterminate outcome for this analysis, and remaining non-successes were classified as having clinical failure, so the trial results did not appear to be influenced by incomplete data capture. Per patient microbiological response rates were likewise ≥90% in both treatment groups across various study visits in the micro-ITT analysis set. There were no clinical relapses at the Late Follow-up visit, no cases of microbiological persistence with increasing MICs, no emergent infections, and no deaths in either treatment group.

Table 22: Favorable Clinical Response by Visit (ITT, Micro-ITT, CE, and ME Analysis Sets)

		CAZ-AVI + MTZ			MER		
Visit	Analysis Set	N	n	Favorable Response Rate (95% CIa)	N	n	Favorable Response Rate (95% CIa)
End of 72 Hours	ITT	61	57	93.4 (85.2, 97.7)	22	20	90.9 (73.9, 98.1)
	Micro-ITT	50	47	94.0 (84.8, 98.3)	19	18	94.7 (77.9, 99.4)
	CE at 72 hours	49	48	98.0 (90.9, 99.8)	20	19	95.0 (78.9, 99.5)
	ME at 72 hours	33	32	97.0 (86.7, 99.7)	15	15	100.0 (84.8, 100.0)
End of IV Treatment	ITT	61	59	96.7 (89.9, 99.3)	22	22	100.0 (89.3, 100.0)
	Micro-ITT	50	48	96.0 (87.8, 99.2)	19	19	100.0 (87.8, 100.0)
	CE at EOIV	54	53	98.1 (91.7, 99.8)	20	20	100.0 (88.3, 100.0)
	ME at EOIV	40	39	97.5 (88.9, 99.7)	15	15	100.0 (84.8, 100.0)
End of Treatment	ITT	61	56	91.8 (83.0, 96.8)	22	22	100.0 (89.3, 100.0)
	Micro-ITT	50	45	90.0 (79.5, 96.1)	19	19	100.0 (87.8, 100.0)
	CE at EOT	52	49	94.2 (85.4, 98.3)	20	20	100.0 (88.3, 100.0)
	ME at EOT	36	33	91.7 (79.4, 97.6)	15	15	100.0 (84.8, 100.0)
Test of Cure	ITT	61	56	91.8 (83.0, 96.8)	22	21	95.5 (80.7, 99.5)
	Micro-ITT	50	45	90.0 (79.5, 96.1)	19	18	94.7 (77.9, 99.4)
	CE at TOC	56	52	92.9 (83.9, 97.5)	20	19	95.0 (78.9, 99.5)
	ME at TOC	40	36	90.0 (78.0, 96.5)	15	14	93.3 (72.8, 99.3)
Late Follow-up	ITT	61	56	91.8 (83.0, 96.8)	22	21	95.5 (80.7, 99.5)
	Micro-ITT	50	45	90.0 (79.5, 96.1)	19	18	94.7 (77.9, 99.4)
	CE at LFU	48	48	100.0 (94.9, 100.0)	18	18	100.0 (87.1, 100.0)
	ME at LFU	37	33	89.2 (76.3, 96.2)	14	13	92.9 (71.2, 99.2)

Source: Study D4280C00015 Clinical Study Report, Table 27.
Notes: The denominator for percentages is the total number of patients in the respective Analysis Set at the given visit, denoted by N within each section. A favorable clinical outcome (for which the count is indicated by n) was defined as clinical cure, sustained clinical cure (only defined at the late follow-up visit), or clinical improvement (only defined at the End of 72 Hour or EOIV visits). CAZ-AVI + MTZ = ceftazidime-avibactam plus metronidazole; CE = clinically evaluable; CI = confidence interval; EOIV = end of intravenous treatment; EOT = end of treatment; ITT = intent-to-treat; IV = intravenous; LFU = late follow-up; ME = microbiologically evaluable. MER = meropenem; micro-ITT = microbiological intent-to-treat; TOC = test of cure.
[a.] Jeffrey's method was used to calculate the two-sided 95% confidence intervals.

Table 23: Per Patient Favorable Microbiological Response by Visit (Micro-ITT Analysis Set)

Visit	Favourable Response; n (%)	
	CAZ-AVI +MTZ N = 50	MER N = 19
EOIV	48 (96.0)	19 (100)
EOT	45 (90.0)	19 (100)
TOC	45 (90.0)	18 (94.7)
LFU	45 (90.0)	18 (94.7)

Source: Study D4280C00015 Clinical Study Report, Table 30.
Notes: The denominator for percentages is the number of patients in the micro-ITT analysis set within each treatment group. CAZ-AVI + MTZ = ceftazidime-avibactam plus metronidazole; EOIV = end of intravenous treatment; EOT = end of treatment; LFU = late Follow-up; MER = meropenem; micro-ITT = microbiological intent-to-treat; TOC = test of Cure.

Findings in Special/Subgroup Populations

The table below shows rates of clinical cure at the TOC visit in demographic subgroups of the ITT analysis set. Results for other subgroups are not shown due to the small sample size in this trial. The most notable observation was that all 4 clinical failures (and 1 indeterminate) in the ceftazidime-avibactam group occurred in the cohort of patients ≥12 years old, while all patients in this cohort treated with meropenem had clinical cure. However, the difference in cure rates between treatment arms in this cohort did not reach nominal statistical significance. Due to the small sample sizes, consideration of multiple subgroups, and inconclusive results, there is not a strong statistical basis for an efficacy concern in this pediatric age cohort.

Table 24: Clinical Cure at the TOC Visit in Demographic Subgroups (ITT Analysis Set)

	Ceftazidime-avibactam plus metronidazole (n = 61)	Meropenem (n = 22)
Age Cohort		
Cohort 1: 12 years to <18 years	17/22 (77.3%)	8/8 (100.0%)
Cohort 2: 6 years to <12 years	33/33 (100.0%)	9/10 (90.0%)
Cohort 3: 2 years to <6 years	6/6 (100.0%)	3/3 (100.0%)
Cohort 4a: 1 year to <2 years	0/0	1/1 (100.0%)
Cohort 4b: 3 months to <1 year	0/0	0/0
Sex		
Female	15/17 (88.2%)	12/13 (92.3%)
Male	41/44 (93.2%)	9/9 (100.0%)
Race		
American Indian or Alaska native	0/1 (0.0%)	0/0
Asian	6/7 (85.7%)	4/4 (100.0%)
Black or African American	0/0	0/0

Native Hawaiian or Pacific Islander	0/0	0/0
Other	0/0	2/2 (100.0%)
White	50/53 (94.3%)	15/16 (93.8%)
Ethnicity		
Hispanic or Latino	11/12 (91.7%)	1/1 (100.0%)
Non-Hispanic or Latino	45/49 (91.8%)	20/21 (95.2%)
Country of Enrollment		
Czech Republic	7/7 (100.0%)	5/5 (100.0%)
Greece	2/2 (100.0%)	2/3 (66.7%)
Hungary	12/14 (85.7%)	1/1 (100.0%)
Poland	1/1 (100.0%)	0/0
Romania	1/1 (100.0%)	1/1 (100.0%)
Russia	2/3 (66.7%)	0/0
Turkey	6/6 (100.0%)	1/1 (100.0%)
Taiwan	5/6 (8.3%)	4/4 (100.0%)
Spain	13/14 (92.9%)	2/2 (100.0%)
United States	7/7 (100.0%)	5/5 (100.0%)

Source: Statistical reviewer.
Notes: The ITT analysis set coincided with the safety analysis set.

MO Comment: The following clinical failure cases (see below table) were reviewed at the statistical reviewer's request to ensure that there were no concerning patterns. The only pattern noted was that the failures all had a diagnosis of perforated appendicitis, which is not meaningful because it was the most common diagnosis in the study. Because the AVYCAZ treatment failures were all in Cohort 1, Clinical Pharmacology has been asked to review the dosing for this age group (see section 6.2 of this review).

Table 25: Summary of ITT analysis set of patients who were clinical failures at TOC

Subject	Site/country	Age	Sex	Arm	Diagnosis	Pertinent Medical History
(b) (6)	05041/ Hungary	15y	F	Avycaz	Appendiceal perforation, appendectomy	n/a
	05041/ Hungary	14y	M	Avycaz	Appendiceal perforation, appendectomy	n/a
	05120/ Taiwan	12y	F	Avycaz	Appendiceal perforation	Obesity, sinusitis
	05181/ Russia	12y	M	Avycaz	Appendiceal perforation, abscess,	n/a

					peritonitis, laparoscopic appendectomy and resection of omentum	
(b) (6)	05267/ Greece	11y	F	Meropenem	Appendiceal perforation, appendectomy	n/a

Source: Clinical Reviewer

7.2.2 Pediatric cUTI Study D4280C00016

Trial Design and Endpoints

The primary objective of Study D42800016 was to evaluate the safety and tolerability of ceftazidime-avibactam at the selected dose regimen versus cefepime in pediatric patients aged ≥3 months to <18 years with cUTI. Secondary objectives were to evaluate descriptive efficacy and to evaluate pharmacokinetics.

Patients were randomized to ceftazidime-avibactam versus cefepime in a 3:1 ratio, and received intravenous treatment for a minimum of 72 hours before having the option for oral switch therapy on Day 4. The age, weight, and renal function dependent dosing of ceftazidime-avibactam matched the dosing in the cIAI trial. Details of cefepime dosing are described in the protocol.

The switch to oral therapy on or after Day 4 was based on Investigator discretion, if the patient had good or sufficient clinical response and was tolerating oral fluids or food. The options for oral therapy (in all cases depending on local guidelines) included ciprofloxacin, cefixime, amoxicillin/clavulanic acid, sulfamethoxazole/trimethoprim, or pathogen-based therapy (in discussion with the Medical Monitor).

The total duration of treatment (intravenous and oral) was to be 7-14 days, and within this window was largely at Investigator discretion.

Like the cIAI trial, this cUTI trial was observer blinded. Each investigator site was to have 1 Blinded Observer without knowledge of treatment assignment. The Blinded Observer was to perform clinical assessments and causality assessments for adverse events.

The planned post-baseline study visits included assessments at the end of intravenous treatment (EOIV), at the end of treatment (EOT), a test of cure (TOC) visit 8 to 15 days after the last dose of any intravenous or oral study drug, and a late follow-up (LFU) visit 20-36 days after the last dose of any intravenous or oral study drug.

The planned sample size in this cUTI trial was 80 evaluable patients, comprising a minimum of 60 and 20 patients in the ceftazidime-avibactam and cefepime groups. For this purpose, an evaluable patient was defined as having completed at least 72 hours of study treatment. A minimum number of evaluable patients was specified for different age cohorts as follows:

- Cohort 1: At least 6:2 evaluable patients aged from 12 years to <18 years;
- Cohort 2: At least 6:2 evaluable patients aged from 6 years to <12 years;
- Cohort 3: At least 9:3 evaluable patients aged from 2 years to <6 years;
- Cohort 4a: At least 9:3 patients aged from 1 year to <2 years;
- Cohort 4b: At least 6:2 patients aged from 3 months to <1 year, with a minimum of 3 patients with at least 1 pharmacokinetic sample aged 3 months to <6 months treated with ceftazidime-avibactam.

The primary outcome variables for assessing safety and tolerability were: adverse events and serious adverse events; cephalosporin class effects and additional adverse events of special interest; vital signs (pulse, blood pressure, respiratory rate, temperature); electrocardiogram; physical examinations; laboratory parameters; and creatinine clearance.

Like the cIAI trial, a secondary purpose of this cUTI study was to evaluate efficacy. The efficacy outcome measures were as follows:

- Clinical response at the end of 72 hours of treatment, EOIV, EOT, and TOC;
- Microbiological response at EOIV, EOT, TOC, and LFU;
- Clinical relapse at LFU;
- Emergent infections;
- Combined clinical and microbiological response.

The tables below define clinical and microbiological outcomes in greater detail for selected study visits.

Table 26: Clinical Outcome Assessments at the End of Intravenous Treatment

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cUTI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Improvement	Patients who switch to oral therapy and meet all of the following criteria at EOIV: • Afebrile (temperature ≤38.0°C) for at least 24 hours • Absence of new and improvement in at least 1 symptom or sign (ie, fever, pain, tenderness, elevated WBCs, elevated CRP) from Baseline and worsening of none
Clinical Failure[a]	Patients who meet any of the following criteria: • Discontinuation of study drug due to insufficient therapeutic effect, including persistence, incomplete clinical resolution, or worsening in signs and symptoms of cUTI that requires alternative non-study antimicrobial therapy; • Discontinuation of study drug due to an AE and requirement for alternative non-study antimicrobial therapy for cUTI; • Death in which cUTI is contributory.
Indeterminate[b]	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00016 Clinical Study Report, Table 6.
Notes: [a.] A clinical failure at EOIV was carried forward to EOT and TOC.
[b.] Any prophylactic systemic antibiotic medication use after first dose until the EOIV assessment would have resulted in a clinical outcome of Indeterminate.
CRP = C-reactive protein; WBC = white blood cell.

Table 27: Clinical Outcome Assessments at the Test of Cure

Outcome	Definition
Clinical Cure	Resolution of all acute signs and symptoms of cUTI or improvement to such an extent that no further antimicrobial therapy is required
Clinical Failure	Patients who meet either of the following criteria: • Incomplete resolution or worsening of cUTI signs or symptoms or development of new signs or symptoms requiring alternative non-study antimicrobial therapy; • Death in which cUTI is contributory.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: • Death in which cUTI is clearly non-contributory; • Extenuating circumstances precluding classification as a cure or failure (eg, patient lost to follow-up).

Source: Study D4280C00016 Clinical Study Report, Table 8.
Notes: Prophylactic systemic antibiotic medication initiated after the EOT assessment did not impact clinical outcome at TOC.

Table 28: Microbiological Outcome Definitions

Outcome	Definition
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Persistence with increasing MICa	Source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥4-fold larger than that observed for the baseline pathogen
Indeterminate	Source specimen was not available to culture

Source: Study D4280C00016 Clinical Study Report, Table 10.
Notes: [a.] Persistence with increasing MIC is a subset of the persistence outcome.
MIC = minimum inhibitory concentration.

Inclusion and Exclusion Criteria

The following inclusion criteria were used for the cUTI trial:

1. Patients must have been ≥3 calendar months to <18 years of age. Patients aged ≥3 calendar months to <1 year must have been born at term (defined as gestational age ≥37 weeks).
2. Written informed consent from parent(s) or other legally acceptable representative(s), and informed assent from patient (if age appropriate according to local regulations).
3. For females who had reached menarche, or had reached Tanner stage 3 development, the patient was authorized to participate in this clinical study if contraceptive criteria (specified in the protocol) were met.
4. Patient had a clinically suspected and/or bacteriologically documented cUTI or acute pyelonephritis judged by the Investigator to be serious and required the patient to be hospitalized for treatment with intravenous therapy.
5. Patient had pyuria:
   - Cohorts 1 to 3 as determined by a midstream clean catch or clean urethral catheterization urine specimen with ≥10 WBCs per high-power field on standard examination of urine sediment or ≥10 WBCs/mm^3 in unspun urine.
   - Cohorts 4a and 4b as determined by a midstream clean catch or clean urethral catherization urine specimen, or urine specimen obtained using urine collection pads (or supra-pubic collection if standard procedure in the assigned sites) ≥5 WBCs per high-power field on standard examination of urine sediment or ≥5 WBCs/mm^3 in unspun urine.
6. Patient had a positive urine culture: 1 midstream clean catch or clean urethral catherization urine specimen taken within 48 hours of randomization containing ≥10^5 CFU/mL of a recognized uropathogen known to be susceptible to the intravenous study therapies (ceftazidime-avibactam and cefepime).
   - If patients met all of the entry criteria except for positive urine culture as outlined above, the patients may have been enrolled before urine culture results were available if the results were likely (based on urinalysis and clinical findings) to be positive and study drugs were considered appropriate empiric therapy. If a patient's urine culture was negative after 24 or 48 hours of treatment but the patient was improving, the Investigator could keep the patient on treatment. If the urine culture

was negative and the patient was not improving, study treatment was to be stopped, and the patient was to be followed for the rest of the study including undergoing all safety assessments until LFU.

7. Demonstrated either acute pyelonephritis or complicated lower urinary tract infection as defined by the following criteria:
    - Patients must have had at least 1 of the following signs/symptoms that had onset or worsened within 7 days of enrollment, in addition to pyuria:
        - Dysuria (including perceived dysuria as referred by parent/caregiver);
        - Urgency;
        - Frequency;
        - Abdominal pain;
        - Fever defined as oral temperature >38.5°C (or equivalent by other methods) with or without patient symptoms or rigor, chills, warmth;
        - Nausea;
        - Vomiting;
        - Irritability;
        - Loss of appetite;
        - Flank pain.
    - Or, patients considered to have complicated UTI as indicated by 2 of the previous qualifying signs/symptoms above plus at least 1 complicating factor from the following:
        - Recurrent UTI (2 or more within 12 months period);
        - Obstructive uropathy that is scheduled to be surgically relieved during intravenous study therapy and before the end of treatment;
        - Functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder;
        - Vesicoureteral reflux;
        - Use of intermittent bladder catherization or presence of an indwelling bladder catheter for >48 hours prior to the diagnosis of cUTI;
        - Urogenital procedure (e.g., cystoscopy or urogenital surgery) within 7 days prior to study entry.

Patients were ineligible for the study if they met any of the following exclusion criteria:

1. Involvement in the planning and/or conduct of the study (applies to both Sponsor staff and/or staff at the study site).
2. Previous enrollment or randomization in the study.
3. Participation in another clinical study with an IP during the last 30 days before the first dose of intravenous study drug or have previously participated in the current study or in another study of ceftazidime-avibactam (in which an active agent was received).
4. History of hypersensitivity reactions to carbapenems, cephalosporins, penicillins, or other beta-lactam antibiotics.

5. Concurrent infection, including, but not limited to, central nervous system infection requiring systemic antibiotics in addition to the intravenous study drug therapy at the time of randomization.
6. Receipt of more than 24 hours of any systemic antibiotics after culture and before study drug therapy.
7. Receipt of systemic antibiotics within 24 hours before obtaining the study-qualifying pre-treatment baseline urine sample and before study drug therapy.
8. The child was suspected or documented to have an infection caused by organisms resistant to the prophylactic antibiotics.
9. A permanent indwelling bladder catheter or instrumentation including nephrostomy or current urinary catheter that would not be removed or anticipation of urinary catheter placement that would not be removed during the course of intravenous study drug therapy administration.
10. Patient had suspected or known complete obstruction of any portion of the urinary tract, perinephric abscess, or ileal loops.
11. Patient had trauma to the pelvis or urinary tract.
12. Patient had undergone renal transplantation.
13. Patient had a condition or history of any illness that, in the opinion of the Investigator, would have made the patient unsuitable for the study (e.g., may have confounded the results of the study or posed additional risk in administering the study therapy to the patient).
14. Patient was considered unlikely to survive the 6 to 8 week study period or had a rapidly progressive illness, including septic shock that was associated with a high risk of mortality.
15. At the time of randomization, patient was known to have a cUTI caused by pathogens resistant to the antimicrobials that were planned to be used in the study.
16. Presence of any of the following clinically significant laboratory abnormalities:
    a. Hematocrit <25% or hemoglobin <8 g/dL (<80 g/L, <4.9 mmol/L);
    b. Serum alanine aminotransferase or aspartate aminotransferase >3 x the age-specific upper limit of normal (ULN), or total bilirubin >2 x ULN (except known Gilbert's disease).
17. Creatinine clearance (CrCl) <30 mL/min/1.73 m^2 calculated using the child's measured height (length) and serum creatinine within the updated "bedside" Schwartz formula: CrCl (mL/min/1.73 m^2) = 0.413 x height (length) (cm)/serum creatinine (mg/dL)
18. History of seizures, excluding documented febrile seizure of childhood.
19. If female, currently pregnant or breast feeding.

Statistical Analysis Plan

Both safety and efficacy variables in this cUTI trial were analyzed using descriptive summaries, and there was no hypothesis testing or corresponding adjustments for multiple comparisons. No interim analyses were performed for efficacy. However, a data safety monitoring board reviewed safety results at periodic intervals.

The statistical analysis plan defined the following analysis sets:

- Safety Analysis Set: All randomized patients who received any amount of IV study therapy (i.e., ceftazidime-avibactam or cefepime). For the safety analysis set, patients were included in all outputs according to the study treatment they actually received.
- Safety Evaluable Analysis Set: A subset of the patients in the safety analysis set who received at least 72 hours of study treatment. Each subject's dosing profile was received by unblinded medical personnel to confirm evaluability.
- PK Analysis Set: A subset of the patients in the safety analysis set who had at least 1 ceftazidime and/or avibactam plasma measurement available.
- Intent-to-Treat (ITT) Analysis Set: All patients who were assigned a randomized treatment.
- Microbiological Intent-to-Treat (micro-ITT) Analysis Set: All randomized patients who had at least 1 Gram-negative typical pathogen in the urine at baseline known to cause cUTI and no Gram-positive pathogens in the urine at baseline.
- Clinically Evaluable (CE) Analysis Set: The CE analysis set was defined separately at the end of 72 hours of study treatment, and at each of the EOIV, EOT, TOC, and LFU visits. The CE analysis set included patients who met all of the following specific conditions:
    - Patients in the micro-ITT analysis set who have received intravenous study therapy and had a confirmed diagnosis of cUTI;
    - Have received at least 48 hours of IV study drug, unless discontinued due to a treatment-limiting adverse event;
    - At the specific visit had a clinical response of cure, improvement, or failure (or have been assessed as a clinical failure before the planned assessment visit), or for LFU were evaluated with a clinical response of sustained cure or relapse;
    - Had no important protocol deviations that would affect assessment of efficacy;
    - Did not receive concomitant antibiotics which would impact assessment of efficacy. This did not include antibiotic therapy taken for the treatment of cUTI by patients who were considered clinical failures.
- Microbiologically Evaluable (ME) Analysis Set: The ME analysis set was defined separately at each of the EOIV, EOT, TOC, and LFU visits. It was similar to the CE analysis set, but required a microbiological response other than indeterminate rather than a clinical response other than indeterminate. Patients also were to have at least 1 typical Gram-negative bacterial pathogen isolated from an adequate baseline microbiological specimen in urine that was susceptible to both ceftazidime-avibactam and cefepime. The statistical analysis plan defined specific criteria for determination of susceptibility.

The safety analysis set was used by the applicant for all safety summaries, unless otherwise specified. The ITT analysis set was defined for efficacy analysis, but closely matched the safety analysis set. There was only one ITT patient in each treatment group excluded from the safety analysis set due to not receiving study drug, and hence these very small numbers did not influence efficacy study conclusions.

Protocol Amendments

The original protocol was amended three times. The amendments were considered relatively minor and did not affect the interpretation of the study results. The first protocol amendment divided Cohort 4 into 4a and 4b, added the requirement that patients in Cohort 4b were to have gestational age ≥37 weeks, added a time window of 8 hours for conducting assessments after 72 hours of treatment, added flank pain as a symptom of cUTI, allowed inclusion of patients with moderate renal impairment, added specific exclusion criteria related to immunocompromised patients, required that creatinine clearance was to be calculated at time points when serum creatinine was being assessed as part of the clinical chemistry panel, revised timelines for urine culture, and made changes to wording and terminology. The second protocol amendment removed specific criteria related to immunocompromised patients that had been added at amendment 1, clarified several aspects of analysis set definitions, added a combined responder outcome including clinical and microbiological response, clarified the definitions for minimum treatment duration, and added other minor changes. The third protocol amendment contained only administrative changes.

Compliance with Good Clinical Practices

The applicant states that *"This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents."*

Financial Disclosure

There were no significant financial conflicts of interest identified among the study site investigators. Please see section 15.2 of this review

Patient Disposition

The subsequent table displays the disposition of patients in the cUTI trial. There were 68 patients randomized to the ceftazidime-avibactam group and 29 patients randomized to the cefepime group. Approximately 7% of patients were prematurely withdrawn from the study. Unlike the cIAI trial, enrollment in this study was well balanced between the age cohorts. The subsequent table also displays membership in various analysis sets. The ITT analysis set almost completely overlapped with the safety analysis set. Approximately 80% of patients in each treatment group belonged to the micro-ITT analysis set with a baseline pathogen, and approximately 70% of patients in each treatment group were considered clinically evaluable at the TOC visit.

Table 29: Patient Disposition

	Number (%) of patients														
	Cohort/Treatment Group														
	Cohort 1			Cohort 2			Cohort 3			Cohort 4			All Cohorts		
	CAZ-AVI (N = 13)	CEF (N = 6)	Total (N = 19)	CAZ-AVI (N = 17)	CEF (N = 5)	Total (N = 22)	CAZ-AVI (N = 11)	CEF (N = 7)	Total (N = 22)	CAZ-AVI (N = 27)	CEF (N = 11)	Total (N = 38)	CAZ-AVI (N = 68)	CEF (N = 29)	Total (N = 101)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients randomised	13	6	19 (100)	17	5	22 (100)	11	7	18 (81.8)	27	11	38 (100)	68	29	97 (96.0)
Patients who were not randomised			0			0			4 (18.2)			0			4 (4.0)
Patients who received IV study treatment	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	11 (100)	7 (100)	18 (100)	26 (96.3)	10 (90.9)	36 (94.7)	67 (98.5)	28 (96.6)	95 (97.9)
Patients who were randomised but did not receive IV study treatment	0	0	0	0	0	0	0	0	0	1 (3.7)	1 (9.1)	2 (5.3)	1 (1.5)	1 (3.4)	2 (2.1)
Patients who completed the study up to the TOC visit	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	10 (90.9)	6 (85.7)	16 (88.9)	24 (88.9)	9 (81.8)	33 (86.8)	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed the study up to the LFU visit	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	10 (90.9)	6 (85.7)	16 (88.9)	24 (88.9)	9 (81.8)	33 (86.8)	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed IV study treatment	11 (84.6)	5 (83.3)	16 (84.2)	16 (94.1)	5 (100)	21 (95.5)	11 (100)	5 (71.4)	16 (88.9)	25 (92.6)	10 (90.9)	35 (92.1)	63 (92.6)	25 (86.2)	88 (90.7)
Patients who discontinued IV study treatment	2 (15.4)	1 (16.7)	3 (15.8)	1 (5.9)	0	1 (4.5)	0	2 (28.6)	2 (11.1)	1 (3.7)	0	1 (2.6)	4 (5.9)	3 (10.3)	7 (7.2)
Patient/parent/legal representative decision	0	0	0	0	0	0	0	0	0	1 (3.7)	0	1 (2.6)	1 (1.5)	0	1 (1.0)
Adverse event	2 (15.4)	0	2 (10.5)	1 (5.9)	0	1 (4.5)	0	0	0	0	0	0	3 (4.4)	0	3 (3.1)
Condition under investigation improved/patient recovered	0	1 (16.7)	1 (5.3)	0	0	0	0	0	0	0	0	0	0	1 (3.4)	1 (1.0)
Based on enrolment culture or susceptibility results	0	0	0	0	0	0	0	2 (28.6)	2 (11.1)	0	0	0	0	2 (6.9)	2 (2.1)
Patients who completed study	13 (100)	6 (100)	19 (100)	17 (100)	5 (100)	22 (100)	10 (90.9)	6 (85.7)	16 (88.9)	24 (88.9)	9 (81.8)	33 (86.8)	64 (94.1)	26 (89.7)	90 (92.8)
Patients prematurely withdrawn from study	0	0	0	0	0	0	1 (9.1)	1 (14.3)	2 (11.1)	3 (11.1)	2 (18.2)	5 (13.2)	4 (5.9)	3 (10.3)	7 (7.2)
Parent/Guardian decision	0	0	0	0	0	0	0	0	0	2 (7.4)	0	2 (5.3)	2 (2.9)	0	2 (2.1)
Lack of therapeutic response	0	0	0	0	0	0	0	1 (14.3)	1 (5.6)	0	0	0	0	1 (3.4)	1 (1.0)
Patient lost to follow-up	0	0	0	0	0	0	1 (9.1)	0	1 (5.6)	0	1 (9.1)	1 (2.6)	1 (1.5)	1 (3.4)	2 (2.1)
Other	0	0	0	0	0	0	0	0	0	1 (3.7)	1 (9.1)	2 (5.3)	1 (1.5)	1 (3.4)	2 (2.1)

Source: Study D4280C00016 Clinical Study Report, Table 14.

Notes: Cohort 1: ≥12 years to <18 years of age; Cohort 2: ≥6 years to <12 years of age; Cohort 3: ≥2 years to <6 years of age; Cohort 4: ≥3 months to <24 months of age; Percentages for the patients randomized and patients not randomized use all patients in the cohort as the denominator. Percentages use the number of patients in the ITT analysis set within each treatment group and cohort as the denominator. CAZ-AVI = ceftazidime-avibactam; CEF = cefepime; IV = intravenous; ITT = intent-to-treat; TOC = test of cure; LFU = late follow-up.

Table 30: Analysis Sets

	CAZ-AVI (N = 68) n (%)	CEF (N = 29) n (%)	Total (N = 101) n (%)
ITT	68	29	97
Safety	67 (98.5)	28 (96.6)	95 (97.9)
Safety Evaluable	63 (92.6)	25 (86.2)	88 (90.7)
PK	64 (94.1)	0	64 (66.0)
micro-ITT	54 (79.4)	23 (79.3)	77 (79.4)
CE at End of 72 h	47 (69.1)	21 (72.4)	68 (70.1)
CE at EOIV	52 (76.5)	22 (75.9)	74 (76.3)
CE at EOT	49 (72.1)	19 (65.5)	68 (70.1)
CE at TOC	49 (72.1)	20 (69.0)	69 (71.1)
CE at LFU	44 (64.7)	15 (51.7)	59 (60.8)
ME at EOIV	35 (51.5)	16 (55.2)	51 (52.6)
ME at EOT	39 (57.4)	14 (48.3)	53 (54.6)
ME at TOC	41 (60.3)	16 (55.2)	57 (58.8)
ME at LFU	16 (23.5)	9 (31.0)	25 (25.8)

Source: Study D4280C00016 Clinical Study Report, Table 16.
Notes: Percentages use the number of patients in the ITT analysis set within each treatment group as the denominator. CAZ-AVI = ceftazidime-avibactam; CE = clinically evaluable; CEF = cefepime; EOIV = end of intravenous treatment; EOT = end of treatment; h = hours; ITT = intent-to-treat; LFU = late follow-up; ME = microbiologically evaluable; micro-ITT = microbiological ITT; N/n = number of patients; PK = pharmacokinetic; TOC = test of cure.

Protocol Violations/Deviations

The table below displays the applicant's summary of important protocol deviations. The most frequently recorded deviations were in the categories of "Lab/Endpoint Data" (21.1% of subjects) and "Assessment Safety" (20.0% of all subjects). The applicant states that within these two categories "The majority of protocol deviations were related to assessments not done as per the schedule of activities." Another common category of recorded protocol deviation was "Study Drug" (18.9% of all subjects). The applicant states for this category that "the majority of protocol deviations were related to minor variations in the expected timing of CAZ-AVI infusions (expected every 8 hours +/-30 minutes)." Additional types of protocol deviations were relatively infrequent.

Table 31: The Applicant's Summary of Important Protocol Deviations (Safety Analysis Set)

Important Protocol Deviation Category	CAZ-AVI (N = 67) n (%)	CEF (N = 28) n (%)	Total (N = 95) n (%)
Number of patients with at least one protocol deviation	41 (61.2)	19 (67.9)	60 (63.2)
Lab/Endpoint Data	11 (16.4)	9 (32.1)	20 (21.1)
Assessment Safety	9 (13.4)	10 (35.7)	19 (20.0)
Study Drug	16 (23.9)	2 (7.1)	18 (18.9)
Visit Window	6 (9.0)	4 (14.3)	10 (10.5)
Informed Consent	6 (9.0)	2 (7.1)	8 (8.4)
Other	4 (6.0)	1 (3.6)	5 (5.3)
Exclusion Criteria	2 (3.0)	1 (3.6)	3 (3.2)
Inclusion Criteria	1 (1.5)	1 (3.6)	2 (2.1)
Overdose/Misuse	1 (1.5)	0	1 (1.1)
Prohibited Co-Medication	1 (1.5)	0	1 (1.1)

Source: Study D4280C00016 Clinical Study Report, Table 15.
Notes: Important protocol deviations were defined and identified prior to database lock. Patients with multiple deviations in a single category were counted once for each category. CAZ-AVI = ceftazidime-avibactam. CEF = cefepime.

Demographic Characteristics

The next table displays demographic characteristics of patients in the safety analysis set. The treatment groups appeared balanced with respect to age, and as previously noted there was roughly even representation from all age cohorts. The majority of patients were female, White, and enrolled in Europe.

Table 32: Demographic Characteristics (Safety Analysis Set)

	Ceftazidime-avibactam (n = 67)	Cefepime (n = 28)
Age Cohort		
Cohort 1: 12 years to <18 years	13 (19.4%)	6 (21.4%)
Cohort 2: 6 years to <12 years	17 (25.4%)	5 (17.9%)
Cohort 3: 2 years to <6 years	11 (16.4%)	7 (25.0%)
Cohort 4a: 1 year to <2 years	12 (17.9%)	5 (17.9%)
Cohort 4b: 3 months to <1 year	14 (20.9%)	5 (17.9%)
Sex		
Female	56 (83.6%)	21 (75.0%)
Male	11 (16.4%)	7 (25.0%)
Race		
American Indian or Alaska native	1 (1.5%)	0 (0.0%)
Asian	12 (17.9%)	5 (17.9%)
Black or African American	0 (0.0%)	0 (0.0%)
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)
Other	5 (7.5%)	0 (0.0%)

White	49 (73.1%)	23 (82.1%)
Ethnicity		
Hispanic or Latino	1 (1.5%)	0 (0.0%)
Non-Hispanic or Latino	66 (98.5%)	28 (100.0%)
Country of Enrollment		
Czech Republic	21 (31.3%)	10 (35.7%)
Greece	13 (19.4%)	8 (28.6%)
Hungary	9 (13.4%)	3 (10.7%)
Poland	2 (3.0%)	0 (0.0%)
Romania	1 (1.5%)	0 (0.0%)
Russia	3 (4.5%)	0 (0.0%)
Turkey	4 (6.0%)	1 (3.6%)
Taiwan	12 (17.9%)	5 (17.9%)
United States	2 (3.0%)	1 (3.6%)

Source: Statistical reviewer and Study D4280C00016 Clinical Study Report, Table 14.1.2.1.1.

Other Baseline Characteristics

The table below shows additional baseline characteristics of patients in the trial. Most subjects had estimated creatinine clearance ≥50 mL/min/1.73 m^2, and did not have complicating factors of the urinary tract infections beyond requirements from inclusion criteria. Despite the small sample size in this study, the treatment groups appeared relatively well balanced on baseline factors.

Table 33: Patient Characteristics at Baseline (Safety Analysis Set)

	Ceftazidime-avibactam (n = 67)	Cefepime (n = 28)
Height (cm)		
Mean (Standard Deviation)	108.7 (34.4)	108.9 (37.2)
Median	99.5	97.5
(Minimum, Maximum)	(53, 170)	(60, 177)
Body Mass Index (kg/m^2)		
Mean (Standard Deviation)	18.6 (4.5)	18.5 (4.6)
Median	17.2	18.9
(Minimum, Maximum)	(13, 34)	(11, 27)
Creatinine Clearance (mL/min/1.73 m^2)		
<30	0 (0.0%)	0 (0.0%)
≥30 to <50	1 (1.5%)	1 (3.6%)
≥50 to <80	23 (34.3%)	7 (25.0%)
≥80	43 (64.2%)	20 (71.4%)
Complicating factors		

None	53 (79.1%)	21 (75.0%)
Recurrent UTI	7 (10.4%)	1 (3.6%)
Functional or anatomical abnormality of the urogenital tract	6 (9.0%)	5 (17.9%)
Vesicoureteral reflux	5 (7.5%)	4 (14.3%)
Intermittent bladder catherization	0 (0.0%)	1 (3.6%)
Urological abnormalities		
Yes	9 (13.4%)	6 (21.4%)
No	58 (86.6%)	22 (78.6%)

Source: Study D4280C00016 Clinical Study Report, Table 20.

Notes: Body mass index was not calculated for children <24 months of age (Cohort 4). Height and body mass index responses were the last non-missing values obtained prior to first administration of study medication. Creatinine Clearance results were as recorded on the case report form using the Bedside Schwartz formula. Patients may have been counted in more than one complicating factor category. Percentages were based on the total number of patients in the treatment group.

The subsequent table displays baseline pathogens in the micro-ITT analysis set. The majority of randomized patients had microbiologically confirmed disease. The predominant pathogen in this trial was *E. coli*. There were no Gram-negative pathogens other than Enterobacteriaceae. No isolates were non-susceptible *in vitro* to ceftazidime-avibactam. There were two patients in the ceftazidime-avibactam group and one patient in the cefepime group that were reported as having *E. coli* isolates non-susceptible to both cefepime and ceftazidime (i.e., without the avibactam inhibitor). Thus, the large majority of patients in the trial had isolates that were susceptible *in vitro* to both study drugs, and resistance did not impact efficacy conclusions.

Table 34**: Baseline Aerobic Gram-Negative Uropathogens (Micro-ITT Analysis Set)**

Pathogen Group **Pathogen**	**CAZ-AVI** **(N = 54)**	**CEF** **(N = 23)**	**Total** **(N = 77)**
Enterobacteriaceae	54 (100)	23 (100)	77 (100)
Citrobacter freundii complex	0	1 (4.3)	1 (1.3)
Enterobacter cloacae	1 (1.9)	0	1 (1.3)
Escherichia coli	49 (90.7)	22 (95.7)	71 (92.2)
Klebsiella pneumoniae	2 (3.7)	0	2 (2.6)
Proteus mirabilis	2 (3.7)	0	2 (2.6)

Source: Study D4280C00016 Clinical Study Report, Table 21.
Notes: A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Likewise, patients with multiple isolates within the same pathogen group were counted only once for that pathogen group.
CAZ-AVI = ceftazidime-avibactam; CEF = cefepime; micro-ITT = microbiological intent-to-treat.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The applicant reports that "Treatment compliance over the entire treatment period was defined as the number of infusions over all doses received, divided by the number of infusions over all doses expected during the treatment period, then multiplied by 100." By this measure, the mean and median treatment compliance rates were 100% across both treatment groups.

As previously noted, oral switch therapy was permitted in this trial. However, additional concomitant systemic antibiotics were not permitted through the LFU visit, and patients requiring such antibacterial treatments for treatment of the cUTI were considered treatment failures.

Efficacy Results

The subsequent tables display rates of favorable clinical response and microbiological response for the ceftazidime-avibactam and cefepime groups, across various analysis populations and study visits. In general, response rates were high in both groups, and numerical trends did not point to any specific efficacy concern for ceftazidime-avibactam. For the TOC clinical response in the ITT analysis set, 4 of the 9 non-successes in the ceftazidime-avibactam group were clinical failures, and 3 of the 5 non-successes in the cefepime group were clinical failures. The remaining patients with non-success were classified as having indeterminate clinical outcomes.

Table 35: Favorable Clinical Response by Visit and Treatment Group (ITT, micro-ITT, CE, and ME Analysis Sets by Visit)

Visit	Analysis Set	CAZ-AVI			CEF		
		N	n	Favorable Response Rate (95% CI[a])	N	n	Favorable Response Rate (95% CI[a])
End of 72 Hours	ITT	68	60	88.2 (79.0, 94.3)	29	25	86.2 (70.5, 95.2)
	micro-ITT	54	49	90.7 (80.9, 96.4)	23	22	95.7 (81.4, 99.5)
	CE at 72 hours	47	47	100 (94.8, 100)	21	20	95.2 (79.8, 99.5)
End of IV Treatment	ITT	68	62	91.2 (82.7, 96.2)	29	26	89.7 (74.9, 97.0)
	micro-ITT	54	52	96.3 (88.6, 99.2)	23	22	95.7 (81.4, 99.5)
	CE at EOIV	52	51	98.1 (91.4, 99.8)	22	21	95.5 (80.7, 99.5)
	ME at EOIV	35	35	100 (93.1, 100)	16	16	100 (85.7, 100)
End of Treatment	ITT	68	60	88.2 (79.0, 94.3)	29	26	89.7 (74.9, 97.0)
	micro-ITT	54	49	90.7 (80.9, 96.4)	23	22	95.7 (81.4, 99.5)
	CE at EOT	49	48	98.0 (90.9, 99.8)	19	18	94.7 (77.9, 99.4)
	ME at EOT	39	39	100 (93.8, 100)	14	14	100 (83.8, 100)
Test of Cure	ITT	68	59	86.8 (77.2, 93.2)	29	24	82.8 (66.3, 93.1)
	micro-ITT	54	48	88.9 (78.5, 95.2)	23	19	82.6 (63.8, 93.8)
	CE at TOC	49	46	93.9 (84.6, 98.2)	20	17	85.0 (65.1, 95.6)
	ME at TOC	41	38	92.7 (81.7, 97.9)	16	14	87.5 (65.6, 97.3)
Late Follow-up	ITT	68	55	80.9 (70.4, 88.8)	29	24	82.8 (66.3, 93.1)
	micro-ITT	54	44	81.5 (69.6, 90.1)	23	19	82.6 (63.8, 93.8)
	CE at LFU	44	41	93.2 (82.9, 98.0)	15	15	100 (84.8, 100)
	ME at LFU	16	12	75.0 (50.9, 90.9)	9	6	66.7 (34.8, 89.6)

Source: Study D4280C00016 Clinical Study Report, Table 25.
Notes: The denominator for percentages is the total number of patients in the respective Analysis Set at the given visit, denoted by N within each section. A favorable clinical outcome (for which the count is indicated by n) was defined as clinical cure, sustained clinical cure, or clinical improvement. CAZ-AVI = ceftazidime-avibactam; CE = clinically evaluable; CEF = cefepime; CI = confidence interval; EOIV = End of intravenous treatment; EOT = End of treatment; ITT = intent-to-treat; IV = intravenous; LFU = Late Follow-up; ME = microbiologically evaluable; micro-ITT = microbiological intent-to-treat; TOC = Test of Cure.

a. Jeffrey's method was used to calculate the two-sided 95% confidence intervals.

The ceftazidime-avibactam group had numerically higher rates of favorable microbiological response across various study visits. Favorable response rates were generally low in both treatment groups at the LFU visit, but this was primarily due to indeterminate responses of approximately 60% in each group. Source specimens were often unavailable for culture at the LFU visit because this visit could be performed by telephone for patients who did not experience clinical relapse or have ongoing or newly developing adverse events.

Table 36: Per Patient Favorable Microbiological Response by Visit and Treatment Group (Micro-ITT Analysis Set)

Visit	Favourable Response; n (%)	
	CAZ-AVI N = 54 n (%)	CEF N = 23 n (%)
EOIV	44 (81.5)	18 (78.3)
EOT	45 (83.3)	17 (73.9)
TOC	43 (79.6)	14 (60.9)
LFU	16 (29.6)	4 (17.4)

Source: Study D4280C00016 Clinical Study Report, Table 28.
Notes: The denominator for percentages is the number of patients in the micro-ITT analysis set. Per patient favorable microbiological response is defined as eradication of all pathogens. CAZ-AVI = ceftazidime-avibactam; CEF = cefepime; EOIV = end of intravenous treatment; EOT = end of treatment; LFU = Late follow-up; micro-ITT = microbiological intent-to-treat; N/n = number of patients; TOC = test of cure.

The primary efficacy endpoint recommended in the FDA guidance on cUTI trials in adults (available at https://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf) is combined clinical and microbiological response. This endpoint defines a favorable outcome for each patient by requiring both a favorable clinical response and a favorable microbiological response. Further, the primary efficacy analysis of this endpoint is conducted in the micro-ITT analysis set, because the microbiological response component cannot be well-defined unless restricting to patients with baseline pathogens. For agents that do not have oral formulations, the FDA guidance recommends co-primary analyses at an early timepoint (preferably defined in a post-randomization window corresponding to the anticipated end of intravenous therapy) and a test of cure visit following anticipated completion of intravenous and oral therapy.

In the pediatric cUTI Study D4280C00016 under review, favorable combined response rates in the micro-ITT analysis set at the EOIV visit were 43/54 (79.6%) in the ceftazidime-avibactam group and 18/23 (78.3%) in the cefepime group. At the TOC visit, rates of favorable combined response were 39/54 (72.2%) in the ceftazidime-avibactam group and 14/23 (60.9%) in the cefepime group. Thus, numerical trends were supportive of ceftazidime-avibactam for the combined response assessment that most closely mirrors the guidance document recommendations. At both the EOIV and TOC timepoints and in each treatment group, between 13%-18% of patients had a combined response classified as indeterminate.

Findings in Special/Subgroup Populations

The table below shows rates of clinical cure at the TOC visit in demographic subgroups of the ITT analysis set. Numerical trends did not generally raise concerns regarding ceftazidime-avibactam efficacy across age cohorts or other demographic groups. However, there was a lower success rate for ceftazidime-avibactam in Cohort 1 of patients 12 to <18 years old, and numerically lower success rates for this cohort were also seen in the cIAI trial. Results in other non-demographic subgroups are not shown, as interpretability was limited due to small sample sizes.

Table 37: Clinical Cure at the TOC Visit in Demographic Subgroups (ITT Analysis Set)

	Ceftazidime-avibactam (n = 68)	Cefepime (n = 29)
Age Cohort		
Cohort 1: 12 years to <18 years	10/13 (76.9%)	6/6 (100.0%)
Cohort 2: 6 years to <12 years	15/17 (88.2%)	5/5 (100.0%)
Cohort 3: 2 years to <6 years	10/11 (90.9%)	6/7 (85.7%)
Cohort 4a: 1 year to <2 years	11/12 (91.7%)	4/6 (66.7%)
Cohort 4b: 3 months to <1 year	13/15 (86.7%)	3/5 (60.0%)
Sex		
Female	49/57 (86.0%)	17/22 (77.3%)
Male	10/11 (90.9%)	7/7 (100.0%)
Race		
American Indian or Alaska native	0/1 (0.0%)	0/0
Asian	11/12 (91.7%)	4/5 (80.0%)
Black or African American	0/0	0/0
Native Hawaiian or Pacific Islander	0/0	0/0
Other	5/5 (100.0%)	0/0
White	43/50 (86.0%)	20/24 (83.3%)
Ethnicity		
Hispanic or Latino	1/1 (100.0%)	0/0
Non-Hispanic or Latino	58/67 (86.6%)	24/29 (82.8%)
Country of Enrollment		
Czech Republic	19/21 (90.5%)	8/10 (80.0%)
Greece	11/14 (78.6%)	7/8 (87.5%)
Hungary	9/9 (100.0%)	3/4 (75.0%)
Poland	2/2 (100.0%)	0/0
Romania	1/1 (100.0%)	0/0
Russia	3/3 (100.0%)	0/0
Turkey	2/4 (50.0%)	1/1 (100.0%)
Taiwan	11/12 (91.7%)	4/5 (80.0%)
United States	1/2 (50.0%)	1/1 (100.0%)

Source: Statistical reviewer.

MO Comment: The following clinical failure cases (see below table) were reviewed at the statistical reviewer's request to ensure that there were no concerning patterns. Out of the four AVYCAZ arm failures in the table below, three of them were due to discontinuation due to an AE (discussed in detail in the Safety section). Five out of the 7 failures in the table below had predisposing factors for cUTI such as genitourinary abnormalities, which may mean that they had particularly difficult-to-treat infections. No other patterns were identified. As the success

rate was the lowest for Cohort 1 (similarly in the cIAI study), Clinical Pharmacology has been asked to review the dosing for this age group (see section 6.2 of this review).

Table 38: Summary of ITT analysis set of patients who were clinical failures at TOC

Subject	Site/country	Age	Sex	Arm	Diagnosis	Pertinent Medical History
(b) (6)	06008/USA	17y	F	Avycaz Dis-continued due to AE	Acute pyelonephritis	Benign adrenal mass, constipation, depression, kidney stones, type 2 diabetes
	06080/ Czech Republic	4m	F	Cefepime	Acute pyelonephritis	Pelvic dystopia of left kidney
	06080/ Czech Republic	22m	F	Cefepime	Acute pyelonephritis	n/a
	06120/ Taiwan	6y	M	Avycaz Dis-continued due to AE	cUTI	TOF, spina bifida, neurogenic bladder, VUR, horseshoe kidney, tethered cord
	06120/ Taiwan	26m	F	Cefepime	cUTI	VUR, multicystic kidney, hydronephrosis, Renal dysgenesis, neurogenic bladder
	06222/ Turkey	6y	F	Avycaz	Acute pyelonephritis	Respiratory insufficiency
	06222/ Turkey	16y	F	Avycaz Dis-continued due to AE	cUTI	ADPKD, alopecia, anxiety, depression, hypertension

Source: Clinical Reviewer

7.3. Integrated Review of Effectiveness

Due to differences in disease characteristics and comparators, efficacy analyses in this review were generally performed separately for the cIAI and cUTI pediatric trials.

One exploratory analysis was conducted based on the numerically lower clinical cure rates in the ITT analysis set seen in Cohort 1 of patients 12 to <18 years old. Cure rates in the combined cIAI and cUTI trials were 27/35 (77.1%) in the ceftazidime-avibactam group and 14/14 (100%) in the combined control group, with a difference in cure rates of -22.9% and a 95% confidence interval for the difference from -39.0% to 0.1%. Although this was near the boundary of nominal statistical significance, this should be considered exploratory due to the limitations of post-hoc subgroup analysis. Exploration of the correct dosing in this age cohort may therefore depend on additional PK/PD analysis.

CDTL Comment: The exposure of AVYCAZ is predicted to be higher in patients aged 12 to <18 years than in adults. Thus, a potential reduction in efficacy in this cohort is not likely to be related to drug exposure. The reader is referred to the Clinical Pharmacology section 6.1 of this review.

7.4. Summary and Conclusions

7.4.1. Summary and Conclusions – Statistics

Evaluation of efficacy was a secondary objective in the cIAI and cUTI trials, and was based on descriptive statistics. Each trial randomized approximately 60 patients to the ceftazidime-avibactam group and 20 patients to the comparator group, with the cIAI trial having greater enrollment in older age cohorts and the cUTI trial having more balanced enrollment across age cohorts. Due to the limited sample sizes, it was not possible to precisely characterize treatment effects on efficacy outcomes from a standalone analysis of each trial, and it was not possible to reproduce primary analyses recommended in the FDA guidance document for the adult cIAI indication due to differences in the timing and definitions of efficacy assessments. In each of the cIAI and cUTI trials, there was a numerical trend toward lower clinical cure rates at the TOC visit in patients in the 12 to <18 year age cohort. The results did not point to any particular concern regarding the efficacy of ceftazidime-avibactam, and efficacy is traditionally extrapolated from adults to pediatrics for the indications under review.

7.4.2. Summary and Conclusions - Clinical

Study D4280C00015 compared AVYCAZ + metronidazole to meropenem for treatment of cIAI. The intent-to treat (ITT) population consisted of 83 patients (AVYCAZ plus metronidazole, n=61, meropenem n=22) who were randomized to receive treatment. At the test of cure (TOC) visit in the cIAI study, which occurred 8 to 15 days after the last dose of study drug, the clinical

response rate in the ITT population was 56/61 (91.8%) for AVYCAZ, and 21/22 (95.5%) for meropenem. In the microbiological-ITT (micro-ITT) population, comprised of patients who had a baseline pathogen known to cause cIAI, the favorable response rate was 45/50 (90%) and 18/19 (94.7%) for AVYCAZ and meropenem, respectively. There were no relapses or pathogens that developed an increasing MIC with treatment.

Study D4280C00016 compared AVYCAZ to cefepime for treatment of cUTI. A total of 95 patients with cUTI received study medication (AVYCAZ, n=67, cefepime n=28). At the TOC visit, which occurred 8 to 15 days after the last dose of study drug, the favorable combined clinical and microbiologic response rate in the micro-ITT population was 39/54 (72.2%) for AVYCAZ and 14/23 (60.9%) for cefepime. The individual clinical and microbiological response rates for AVYCAZ were 48/54 (88.9%) and 43/54 (79.6%), respectively, compared to the clinical and microbiological response rates for cefepime of 19/23 (82.6%) and 14/23 (60.9%), respectively. There were 4 clinical relapses in the AVYCAZ group, 3 of which were in patients with urological abnormalities, compared with the cefepime group which had no clinical relapses. There were 3 emergent infections in the AVYCAZ group, 2 of which were in patients with urological abnormalities, compared with the cefepime group with had no emergent infections. There were no persistent pathogens with increasing MIC.

8 Clinical Microbiology Review

8.1. Nonclinical Microbiology

The in-vitro activity of ceftazidime-avibactam was evaluated against 12,984 clinical isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* in pediatric patients (ages < 18 years) with urinary tract infections (UTI) and intra-abdominal infections (IAI). The clinical isolates were collected from 70 medical centers geographically distributed across 9 USA census regions. Clinical isolates collected from patients with IAIs showed that the prevalent causative organisms from pediatric patients were similar to those observed for adults (≥ 18 years). *E. coli* and *Klebsiella* spp. were the most prevalent members of the Enterobacteriaceae followed by *P. aeruginosa*. Among the Enterobacteriaceae, the ceftazidime-avibactam MIC_{90} value was 0.25 µg/mL for children and 0.5 µg/mL for adults. Among the *P. aeruginosa*, the ceftazidime-avibactam MIC90 value was 4 µg/mL for both age cohorts.

Most cases of cUTI and acute pyelonephritis are caused by Enterobacteriaceae, with *E. coli* being the predominant causative pathogen in most infections across age groups accounting for 67.1% of uropathogens from pediatric patients and 48.6% from adults. In comparison, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp. and *P. aeruginosa* accounted for 3.5% of gram-negative UTI isolates from pediatric patients. Among the Enterobacteriaceae and *P. aeruginosa*, the ceftazidime-avibactam MIC_{90} values were 0.25 µg/mL and 2 µg/mL, respectively.

There were no new non-clinical data (in vitro activity or animal studies) that described the activity of ceftazidime-avibactam in this supplement.

8.2. Clinical Microbiology

This section of the review focuses on the microbiologic aspects of the two pediatric Phase 2 studies conducted under PMR#2862-1 and PMR#2862-2, respectively. The purpose was to evaluate the pharmacokinetics, safety and efficacy of ceftazidime-avibactam in order to extend the indications of complicated urinary tract infections (Study# D4280C00016), including pyelonephritis and/or complicated intra-abdominal infections (Study# D4280C0015) in the treatment of pediatric patients ≥ 3 months to < 18 years of age.

The microbiology results for the two studies are provided separately (*for further details on study design and clinical efficacy* see Section 7 Statistical and Clinical Evaluation).

8.2.1. Complicated Intrabdominal Infections (cIAI)

Briefly, the micro-ITT analyses included all randomized patients who had a qualifying baseline pathogen from either intra-abdominal fluid samples (such as tissue or aspirate suitable for isolation of both aerobic and anaerobic bacteria) or blood cultures which could be reasonably implicated as an etiological agent of cIAI. Organism identification and susceptibility testing of

baseline pathogens were determined based on central laboratory data unless unavailable, in which case local laboratory (if available) data was used to identify baseline pathogens. Microbiological response assessments were assessed for each baseline pathogen isolated as follows:

Outcome	Definition
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Presumed eradication	Source specimen was not available to culture, and the patient was assessed as a clinical cure or sustained clinical cure or (for EOIV only) clinical improvement
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Persistence with increasing MIC[a]	Source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥4-fold larger than that observed for the baseline pathogen
Presumed persistence	Source specimen was not available to culture and the patient was assessed as a clinical failure or clinical relapse
Indeterminate	Source specimen was not available to culture and the patient's clinical outcome was assessed as indeterminate

The most frequently reported Enterobacteriaceae pathogen at baseline was *Escherichia coli* (79.7%) whereas *K. pneumoniae* was reported in 4.3% of patients (Table 39). The predominant gram-negative other than Enterobacteriaceae was *P. aeruginosa* (33.3%). No other gram-negative aerobic pathogens were identified in more than 2 patients in any treatment group. A total of 37 patients (53.6%) had gram-positive pathogens identified at baseline; the most frequently reported was *Streptococcus anginosus* (47.8%). The most frequently reported anaerobe was *B. fragilis* (30.4%). The incidences of the pathogens were similar between treatment groups as well as in the microbiological evaluable (ME) group.

Table 39: Summary of most prevalent baseline pathogen (≥2 patients) from intra-abdominal site and/or blood in cIAI patients in Study D4280C00015 (Micro-ITT Analysis Set)

Pathogen Group Pathogen	CAZ AVI + MTZ (N = 50) [n (%)]	MER (N = 19) [n %]	Total (N = 69) [n (%)]
Enterobacteriaceae	**42 (84.0)**	**14 (73.7)**	**56 (81.2)**
Escherichia coli	42 (84.0)	13 (68.4)	55 (79.7)
Klebsiella pneumoniae	2 (4.0)	1 (5.3)	3 (4.3)
Gram-negative other than	**16 (32.0)**	**10 (52.6)**	**26 (37.7)**
Pseudomonas aeruginosa	14 (28.0)	9 (47.4)	23 (33.3)
Gram-positive	**26 (52.0)**	**11 (57.9)**	**37 (53.6)**
Enterococcus avium	4 (8.0)	1 (5.3)	5 (7.2)
Enterococcus faecium	2 (4.0)	0	2 (2.9)
Streptococcus anginosus group	23 (46.0)	10 (52.6)	33 (47.8)
Anaerobes	**24 (48.0)**	**12 (63.2)**	**36 (52.2)**
Bacteroides caccae	3 (6.0)	0	3 (4.3)
Bacteroides fragilis	14 (28.0)	7 (36.8)	21 (30.4)
Bacteroides fragilis group	2 (4.0)	2 (10.5)	4 (5.8)

Pathogen Group Pathogen	CAZ AVI + MTZ (N = 50) [n (%)]	MER (N = 19) [n %]	Total (N = 69) [n (%)]
Bacteroides ovatus	2 (4.0)	0	2 (2.9)
Bacteroides thetaiotaomicron	3 (6.0)	3 (15.8)	6 (8.7)
Bacteroides vulgatus	2 (4.0)	0	2 (2.9)
Clostridium perfringens	0	2 (10.5)	2 (2.9)
Clostridium ramosum	2 (4.0)	0	2 (2.9)
Eggerthella lenta	2 (4.0)	0	2 (2.9)
Parabacteroides distasonis	2 (4.0)	0	2 (2.9)
Parvimonas micra	4 (8.0)	5 (26.3)	9 (13.0)
Prevotella buccae	2 (4.0)	0	2 (2.9)

Source: Study D4280C00015 Clinical Efficacy Summary Table 2.2.1.4-1, CSR, Table 14.1.2.1.5.

Table 40 shows the favorable clinical and microbiological response at TOC by baseline pathogen for the micro-ITT and ME analyses for the indicated pathogens. In the micro-ITT analysis set, favorable clinical responses for infections due to *E. coli* was 90.5% for the ceftazidime-avibactam plus metronidazole group and 92.9% for the meropenem group. Against *P. aeruginosa,* favorable clinical response was 95.7% for the ceftazidime-avibactam plus metronidazole group and 88.9% for the meropenem group. Most microbiological outcomes were presumed eradicated based on clinical response; showing a similar pattern to the per-patient clinical response for predominant pathogens (*E. coli* and *P. aeruginosa*). The results for ME analyses and the micro-ITT population were similar.

Table 40: Favorable clinical response and microbiological eradication/presumed eradication per patient at TOC against baseline cIAI pathogens from intra-abdominal site and/or in Study D4280C00015 (Micro-ITT Population)

Analysis Group	Pathogen Group Pathogen	Favorable Clinical Response		Microbiological Eradication/ Presumed Eradication	
		CAZ-AVI +MTZ n/N* (%)	MER n/N (%)	CAZ-AVI +MTZ n/N* (%)	MER n/N (%)
Micro-ITT	Enterobacteriaceae	38/42 (90.5)	13/14 (92.9)	38/42 (90.5)	13/14 (92.9)
	Escherichia coli	38/42 (90.5)	12/13 (92.3)	3/45 (90.5)	12/13 (92.3)
	Klebsiella pneumoniae	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)
	Other than	14/16 (87.5)	9/10 (90.0)	14/16 (87.5)	9/10 (90.0)
	Pseudomonas aeruginosa	12/14 (85.7)	8/9 (88.9)	12/14 (85.7)	8/9 (88.9)
ME	Enterobacteriaceae	34/38 (89.5)	12/13 (92.3)	34/38 (89.5)	12/13 (92.3)
	Escherichia coli	34/38 (89.5)	11/12 (91.7)	34/38 (89.5)	11/12 (91.7)
	Klebsiella pneumoniae	--	--	1/1 (100.0)	1/1 (100.0)
	Other than	13/14 (92.9)	8/9 (88.9)	13/14 (92.9)	8/9 (88.9)
	Pseudomonas aeruginosa	12/13 (92.3)	8/9 (88.9)	12/13 (92.3)	8/9 (88.9)

*The denominator for percentages is the total number of patients with a baseline pathogen indicated in each row, denoted by N. The number of patients with a favorable clinical cure is represented by n. A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Similarly, patients with multiple isolates with the same pathogen group were counted only once for that pathogen group.
CAZ-AVI= ceftazidime-avibactam; ME = microbiologically evaluable; MER = meropenem; micro-ITT = microbiological intent-to-treat; MTZ = Metronidazole; TOC = Test of Cure
Source: Study D4280C00015 CCSR, 14.1.2.1.15

Table 41 shows the MICs of ceftazidime-avibactam and comparators against baseline pathogens in the micro-ITT population.

- Against *Enterobacteriaceae* isolate, the ceftazidime-avibactam MIC range from ≤0.008 – 0.12 µg/mL with MIC_{90} of 0.12 µg/mL with the *E. coli* isolates as the predominant pathogen showing similar ceftazidime-avibactam MICs. The ceftazidime-avibactam MICs ranged from 0.5 – 8 µg/mL for *P. aeruginosa.* There were no pathogens that had MICs ≥ 8/4 µg/mL for ceftazidime-avibactam.
- The ceftazidime MIC range for *E. coli* was ≤ 0.03 – 32 µg/mL and for *P. aeruginosa* was 0.5 – 4 µg/mL. Two patients in the ceftazidime-avibactam plus metronidazole group infected with *E. coli* had ceftazidime MICs of 16 µg/mL and 32 µg/mL, respectively. There were no ceftazidime resistant isolates in the meropenem treatment group.
- The meropenem MIC were 0.015 – 0.03 µg/mL for *E. coli* and 0.06 – 0.5 µg/mL for *P. aeruginosa.* There were no pathogens that were resistant to meropenem.

Table 41: Activity of ceftazidime-avibactam, ceftazidime and comparator against baseline cIAI pathogens from intra-abdominal site and/or in Study D4280C00015 (Micro-ITT Population)

Pathogen Group Pathogen	Ceftazidime-avibactam MIC* (in µg/mL)				Ceftazidime MIC (in µg/mL)				Meropenem MIC (in µg/mL)			
	N	Range	MIC_{50}	MIC_{90}	N	Range	MIC_{50}	MIC_{90}	N	Range	MIC_{50}	MIC_{90}
Enterobacteriaceae	41	≤0.008 – 0.12	0.12	0.12	41	≤0.03 – 32	0.25	0.25	16	0.015 – 0.03	0.015	0.015
Escherichia coli	39	≤0.008 – 0.12	0.12	0.12	39	≤0.03 – 32	0.25	0.25	13	0.015 – 0.03	0.015	0.015
Klebsiella pneumoniae	2	0.015 – 0.12	--	--	2	0.25	--	--	1	0.03	--	--
Other than												
Pseudomonas aeruginosa	13	0.5 – 4	2	4	13	0.5 – 4	2	4	9	0.06 – 0.5	0.25	0.5

*Avibactam was tested at a fixed concentration of 4 µg/mL
Source: Study D4280C00015 CCSR, Table 14.1.2.1.9, 14.1.2.1.10, 14.1.2.1.11.

Table 42 shows the per-pathogen microbiological response by ceftazidime-avibactam MIC for patients in the micro-ITT and ME populations. Among the *Enterobacteriaceae* isolates the MIC values for ceftazidime ranged from ≤0.008 – 0.12 µg/mL with no trend in unfavorable microbiological outcomes observed over the MIC range. The microbiological response for *P. aeruginosa* isolates were 92.3%, there were no isolates with ceftazidime-avibactam MICs ≥ 8/4 µg/mL.

Table 42: Per pathogen favorable microbiological response rate at TOC by MIC in Study D4280C00015 (Micro-ITT Analysis Set)

Ceftazidime-avibactam MIC (in µg/mL)	Microbiological Eradication (Micro-ITT)	Microbiological Eradication (ME Analysis)
Enterobacteriaceae		
Escherichia coli		
≤0.008	1/1 (100.0)	1/1 (100.0)
0.015	2/2 (100.0)	2/2 (100.0)
0.03	2/3 (66.7)	2/3 (66.7)
0.06	8/10 (80.0)	7/9 (77.8)

Ceftazidime-avibactam MIC (in µg/mL)	Microbiological Eradication (Micro-ITT)	Microbiological Eradication (ME Analysis)
0.12	22/23 (95.7)	22/23 (95.7)
Klebsiella pneumoniae	2/2 (100.0)	1/1 (100.0)
0.015	1/1 (100.0)	--
0.12	1/1 (100.0)	1/1 (100.0)
Other than Enterobacteriaceae		
Pseudomonas aeruginosa	12/13 (92.3)	12/13 (92.3)
0.5	1/1 (100.0)	1/1 (100.0)
1	2/3 (66.7)	2/3 (66.7)
2	6/6 (80.0)	6/6 (80.0)
4	3/3 (100.0)	3/3 (100.0)

Source: Study D4280C00015 CCSR, Table 14.2.1.16, Table 14.2.1.17

In ceftazidime-avibactam plus metronidazole treatment group, there were no reported cases of persistence or persistence showing an increase in ceftazidime-avibactam MIC. In the meropenem group, there was one case of *B. fragilis* isolated at baseline from the abdominal cavity of patient# (b) (6) which was isolated from percutaneous drainage fluid with persistence documented at an unscheduled visit on Day 5. The sample from Day 5 was not submitted and analyzed at the central laboratory.

Concurrent Bacteremia

A total of 2 patients had isolates identified in the blood in the ceftazidime-avibactam treatment group (*E. coli* in Patient# (b) (6) and *P. aeruginosa* in patient# (b) (6)); no patient in the meropenem group had gram-negative pathogens identified in the blood at baseline.

Treatment Emergent Infections

There were no treatment emergent infections reported in either treatment group.

Comparison with adult cIAI studies (cD4280C0001/5)

In the micro-ITT population, the most frequently (>2 subject) isolated organisms at baseline from pediatric subjects was *E. coli* (79.7%); similar to the adult studies which showed 67.6% of patients had *E. coli.* Similarly, the most frequently gram-negative pathogen other than Enterobacteriaeceae reported in pediatrics was *P. aeruginosa* (33.3%) which was consistent with that observed in adults (8.6%). Based on the indicated pathogens, Enterobacteriaceae and *P. aeruginosa*, favorable microbiological response at TOC in the pediatrics ceftazidime-avibactam plus metronidazole group for infections due to *E. coli* was 90.5% and 95.7% against *P. aeruginosa* infections. This was consistent with adult studies which showed ≥ 75.5% for Enterobacteriaceae and ≥ 85.7 % for *P. aeruginosa.* In the pediatric study, all isolates were susceptible to ceftazidime-avibactam. There were 2 patients in the ceftazidime-avibactam plus metronidazole group had ceftazidime resistant isolates, the MICs for the 2 ceftazidime-resistant *E. coli* isolates were 16 µg/mL and 32 µg/mL, respectively, these were favorable responses.

8.2.2. Complicated Urinary Tract Infections (cUTI)

The micro-ITT population included patients with pyuria and positive urine culture (midstream clean catch or clean urethral catherization) taken within 48 hours of randomization containing ≥ 10^5 colony forming units (CFU/mL) of a recognized uropathogens known to be susceptible to the IV study therapy (ceftazidime-avibactam and cefepime). Urine samples were obtained at baseline (before any antimicrobials were administered) and at EOIV, EOT, TOC and LFU. Cultures were repeated per standard of care upon knowledge of a positive result until sterilization was confirmed. In addition, if clinically indicated, blood samples were obtained for culture and routine analysis (including microscopic examination) at baseline (before any antimicrobials were administered) and at any time until LFU. Culture, organism identification and antimicrobial susceptibility testing were performed at the local or regional laboratory to support patient care. All isolates were sent to a central laboratory for organism identification confirmation and antimicrobial susceptibility testing. Antimicrobial susceptibility was conducted using the CLSI reference broth microdilution testing. Microbiological response assessments were assessed for each baseline pathogen isolated as follows:

Outcome	Definition
Eradication	Source specimen demonstrated absence of the original baseline pathogen
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
Persistence with increasing MICa	Source specimen demonstrates continued presence of the original baseline pathogen with an MIC value ≥4-fold larger than that observed for the baseline pathogen
Indeterminate	Source specimen was not available to culture

Source: Study D4280C00016 Protocol Table 12

All patients had Enterobacteriaceae reported at baseline, with 92.2% of patients infected with *E. coli* (Table 43). No patient had a gram-negative uropathogens other than Enterobacteriaceae.

Table 43: Summary of most frequent baseline pathogen (≥ 2 patients) in cUTI patients in Study D4280C00016 (Micro-ITT Analysis Set)

Pathogen Group Pathogen	CAZ AVI N [n (%)]	CEF N [n (%)]	Total N [n (%)]
Enterobacteriaceae	54 (100)	23 (100)	77 (100)
Escherichia coli	49 (90.7)	22 (95.7)	71 (92.2)
Klebsiella pneumoniae	2 (3.7)	0	2 (2.6)
Proteus mirabilis	2 (3.7)	0	2 (2.6)
Enterobacter cloacae	1 (1.9)	0	1 (1.3)
Citrobacter freundii complex	0	1 (4.3)	1 (1.3)
Gram-negative other than Enterobacteriaceae	0	0	0

CAZ-AVI = Ceftazidime-avibactam; CEF = Cefepime

Source: Study D4280C00016 Clinical Efficacy Summary Table 2.2.1.4-1, CSR, Table 14.1.2.1.5.

Table 44 shows the favorable clinical response and microbiological response at TOC visit by baseline pathogen for the indicated pathogens. In the micro-ITT population, for infections due

to *E. coli,* the favorable clinical response was >81% for both treatment groups (87.8% for the ceftazidime-avibactam group and 81.8% for the cefepime group). Microbiological eradication in patients with an infection with *E. coli* was 79.6% for ceftazidime-avibactam group and 59.1% for cefepime group. Overall, the combined response (i.e., favorable combined clinical and microbiological eradication) was 82.2% of patients in the ceftazidime-avibactam group and 60.9% in the cefepime group. The results of the ME analysis were similar to the micro-ITT analysis, most patients had favorable clinical responses at TOC for infections due to *E. coli* (91.9% for the ceftazidime-avibactam group and 86.7% for the cefepime group).

Table 44: Favorable clinical response and microbiological eradication/presumed eradication per patient at TOC against baseline cIAI pathogens from intra-abdominal site and/or in Study D4280C00015 (Micro-ITT Analysis Set)

Analysis Group	Pathogen Group Pathogen	Favorable Clinical Response		Microbiological Eradication/ Presumed Eradication	
		CAZ-AVI n/N* (%)	CEF n/N (%)	CAZ-AVI n/N* (%)	CEF n/N (%)
Micro-ITT	Enterobacteriaceae	48/54 (88.9)	19/23 (82.6)	43/54 (79.6)	14/23 (60.9)
	Escherichia coli	43/49 (87.8)	18/22 (81.8)	39/49 (79.6)	13/22 (59.1)
ME	Enterobacteriaceae	38/41 (92.7)	14/16 (87.5)	36/41 (87.8)	11/16 (68.8)
	Escherichia coli	34/37 (91.9)	13/15 (86.7)	32/37 (86.5)	10/15 (66.7)

*The denominator for percentages is the total number of patients with a baseline pathogen indicated in each row, denoted by N. The number of patients with a favorable clinical cure is represented by n. A patient could have more than 1 pathogen. Multiple isolates of the same species from the same patient were counted only once for that pathogen. Similarly, patients with multiple isolates with the same pathogen group were counted only once for that pathogen group.
CAZ-AVI= ceftazidime-avibactam; ME = microbiologically evaluable; CEF = cefepime; micro-ITT = microbiological intent-to-treat; TOC = Test of Cure
Source: Clinical Efficacy Summary Table 2.2.2.5-1, 2.2.2.7-1; Study D4280C00016 CCSR, 14.1.2.1.14, 14.2.1.15

Table 45 shows the MIC of all baseline pathogens in the cUTI study.

- The ceftazidime avibactam MICs ranged from ≤ 0.015 to 0.5 µg/mL for Enterobacteriaceae and ≤ 0.015 to 0.25 µg/mL against *E. coli* isolates. There were no pathogens that were resistant to ceftazidime-avibactam.
- The ceftazidime MIC range for Enterobacteriaceae was ≤ 0.06 to 64 µg/mL. and ≤ 0.06 to 64 µg/mL against *E. coli*.
- The cefepime MIC range for Enterobacteriaceae was ≤ 0.015 to 16 µg/mL and ≤ 0.015 to 16 µg/mL for *E. coli* was. Two patients in the ceftazidime-avibactam group and 1 patient in the cefepime group had *E. coli* isolates that were resistant to cefepime at baseline.

Table 45: Activity of ceftazidime-avibactam, ceftazidime and comparator for baseline uropathogens in Study D4280C00016 (Micro-ITT Analysis Set)

	Ceftazidime-avibactam MIC* (in µg/mL)				Ceftazidime MIC* (in µg/mL)				Cefepime MIC (in µg/mL)			
Pathogen Group	N	Range	MIC_{50}	MIC_{90}	N	Range	MIC_{50}	MIC_{90}	N	Range	MIC_{50}	MIC_{90}

Enterobacteriaceae	51	≤0.015 – 0.5	0.12	0.25	51	0.06 - 64	0.12	0.5	21	0.015 – > 16	0.06	0.25
Escherichia coli	46	≤0.015 – 0.25	0.12	0.12	46	0.06 – 64	0.12	0.25	20	0.015 – >16	0.06	0.25
Klebsiella pneumoniae	2	0.12 – 0.25	--	--	2	0.12 – 0.5	--	--	0	--	--	--
Proteus mirabilis	2	0.03 – 0.06	--	--	2	0.06	--	--	0	--	--	--
Enterobacter cloacae	1	0.5	--	--	1	1	--	--	0	--	--	--
Citrobacter freundii	0	--	--	--	0	--	--	--	1	0.03	--	--

*Provided for the isolates from patients in the ceftazidime-avibactam treatment group; ** Provided for the isolates from patients in the cefepime treatment group
Source: Study D4280C00015 CCSR, Table 14.1.2.1.9, 14.1.2.1.10, 14.1.2.1.11.

Table 46 shows the per-pathogen microbiological eradication/presumed eradication at TOC by uropathogens. For the predominant pathogen, *E. coli*, there was no indication that increasing MIC was associated with a lower favorable response. There were 2 patients in the ceftazidime-avibactam group infected with ceftazidime resistant *E. coli* (Patient# (b) (6) and Patient# (b) (6)). Patient# (b) (6) had an *E. coli* at baseline resistant to ceftazidime (MIC = 32 µg/mL) and had favorable clinical responses at all time points. Patient# (b) (6) had an *E. coli that* was resistant to ceftazidime (MIC = 64 µg/mL) and had favorable clinical responses at all time points except for the EOT visit, at which the response was indeterminate. The 1 patient in the cefepime group (Patient# (b) (6) infected with ceftazidime resistant *E. coli* isolate and also resistant to cefepime (MIC ≥ 16 µg/mL) was a clinical failure.

Table 46: Per pathogen favorable microbiological response at TOC by ceftazidime-avibactam MIC (Study D4280C00016)

Ceftazidime-avibactam MIC (in µg/mL)	Microbiological Eradication (Micro-ITT)	Microbiological Eradication (ME Analysis)
Enterobacteriaceae		
Escherichia coli	36/46 (78.3)	32/37 (86.5)
0.015	2/2 (100.0)	2/2 (100.0)
0.03	1/1 (100.0)	1/1 (100.0)
0.06	14/19 (73.7)	13/14 (92.9)
0 12	15/20 (75.0)	14/18 (77.8)
0 25	4/4 (100.0)	2/2 (100.0)
Klebsiella pneumoniae	1/2 (50.0)	1/1 (100.0)
0 12	1/1 (100.0)	1/1 (100.0)
Proteus mirabilis	2/2 (100.0)	2/2 (100.0)
0.03	1/1 (100.0)	1/1 (100.0)
0.06	1/1 (100.0)	1/1 (100.0)
Enterobacter cloacae	1/1 (100.0)	1/1 (100.0)
0 5	1/1 (100.0)	1/1 (100.0)

Source: Study D4280C00016 CCSR, Table 14.2.1.16, Table 14.2.1.17

At TOC, there were 5 patients in each treatment group (9.3% [5/54] ceftazidime-avibactam and 21.7% [5/23] cefepime) with persistent Enterobacteriaceae infections. At LFU, there were 11.1% (6/54) patients with persistent pathogens in the ceftazidime-avibactam group and 21.7%

(5/23) in the cefepime group. There were no reported cases of pathogens with reported persistence with increasing MIC in either treatment group.

Concurrent Bacteremia
There were no uropathogens identified in the blood.

Treatment Emergent Infections
A total of 3 patients ([redacted](b) (6)) in the ceftazidime-avibactam group had emergent infections; none occurred in the cefepime group. Of the 3 new infections, 2 patients were reported to have both underlying urological abnormalities and complicating factors.

Comparison to Adult cUTI studies (D4280C0002/4)
The baseline microbiology was similar in the pediatric study compared to adult study with majority of patients infected with *E. coli* (92.2% in pediatric patients vs. 73.8% in adult patients). Overall, favorable microbiological responses in the pediatric population for *E. coli* at TOC were 79.6% in the micro-ITT analysis population compared with 78.4% in the micro-ITT analysis set in the adult study. The predominant pre-therapy organisms isolated from the enrolled pediatric subjects were susceptible to ceftazidime avibactam showing MICs ranging from ≤ 0.015 to 0.25 µg/mL against *E. coli* isolates with MIC_{90} value of 0.12 µg/mL (based on a fixed concentration of 4 µg/mL for avibactam). There were no pathogens that had MICs ≥ 8/4 µg/mL to ceftazidime-avibactam.

8.3. SUMMARY AND CONCLUSIONS

Overall, the microbiological response in pediatric patients and adolescents less than 18 years of age was similar to the adult patients for the indicated pathogens in the Indications and Usage Section of the labeling.

There are no changes to labeling with respect to Clinical microbiology (Section 12.4 Microbiology).

9 Review of Safety

Safety Review Approach

This safety review is based on two Phase 2 single-blind, randomized, multicenter active-controlled studies of pediatric patients aged ≥3 months to 18 years. Study D4280C00015 compared CAZ-AVI + MTZ to meropenem for treatment of cIAI. Study D4280C00016 compared CAZ-AVI to cefepime for treatment of cUTI. Study D4280C00014 was a Phase 1 single-dose PK study to determine dosing and will not be considered in the analysis of safety. An overview of safety is presented in Table 47, below.

Table 47: Summary of Adverse Events up to Last Visit in Any Category – (Safety Analysis Set) Pooled Phase 2 Pediatric Studies D4280C00015 (cIAI) and D4280C00016 (cUTI)

AE Category	*Number (%) of Patients*					
	cIAI		*cUTI*		*Total*	
	CAZ AVI +MTZ (N=61)	*Meropenem (N=22)*	*CAZ AVI (N=67)*	*Cefepime (N=28)*	*CAZ AVI ± MTZ (N=128)*	*Comparator (N=50)*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Any AE	32 (52.5)	13 (59.1)	36 (53.7)	15 (53.6)	68 (53.1)	28 (56.0)
Any AE with an outcome of death	0	0	0	0	0	0
Any SAE	5 (8.2)	1 (4.5)	8 (11.9)	2 (7.1)	13 (10.2)	3 (6.0)
Any AE leading to discontinuation of study drug[a]	0	0	3 (4.5)	0	3 (2.3)	0
Any AE of severe intensity	4 (6.6)	1 (4.5)	6 (9.0)	2 (7.1)	10 (7.8)	3 (6.0)

Patients with multiple AEs in the same category are counted only once in that category. Patients with AEs in more than 1 category are counted once in each of those categories.

Includes AEs with an onset date/time on or after the date/time of first infusion up to and including the last visit.

Percentages are based on the total number of patients in the treatment group (N).

[a] Action taken, study drug permanently discontinued.

Source: Module 5.3.5.3 sNDA, Pooled ISS Table 4.2.2.4.10

9.1.2. Review of the Safety Database

Overall Exposure

In total, 67 pediatric patients were exposed to CAZ-AVI in the cUTI study and 61 pediatric patients were exposed to CAZ-AVI + metronidazole in the cIAI study for a total of 128 patients. A total of 50 patients received the comparator drug, either meropenem or cefepime. There

were more patients in the older age groups in the cIAI study, as demonstrated in Table 48 below. The median age of CAZ-AVI exposed patients was 8.6 years and the median age for the comparator drugs was 7.4 years. The mean duration of exposure to CAZ-AVI was 5.7 days compared to 6 days for the comparator drugs. The two studies were evaluated separately due to differences in the underlying conditions, demographics and exposures of the patients.

Table 48: Exposure to CAZ-AVI by age group

	Patients exposed to CAZ-AVI (N=128)		
Age Cohort	cIAI	cUTI	Total
Cohort 1: 12-<18 years	22	13	35
Cohort 2: 6-<12 years	33	17	50
Cohort 3: 2-<6 years	6	11	17
Cohort 4a: 1-<2 years	0	12	12
Cohort 4b: 3 months-<1 year	0	14	14
Total	61	67	128

Source: Reviewer generated

Relevant characteristics of the safety population:

cIAI

Patients were eligible for the study if they were aged ≥ 3 months to < 18 years and had clinical evidence of cIAI requiring hospitalization and 7-15 days of antibacterial treatment in addition to surgical management. Appendicitis was the most common underlying diagnosis; 86.7% of patients had appendiceal perforation or peri-appendiceal abscess, 10.8% had secondary peritonitis, and 2.4% had traumatic intestinal perforation. Patients were stratified into four age cohorts: 12-18 years, 6-<12 years, 2-<6 years, and 3 months-<2 years (further divided into 1-<2 years and 3 months-<1 year). Patients received either IV CAZ-AVI + metronidazole (MTZ) 10mg/kg or IV meropenem 20mg/kg. Metronidazole was included to provide anaerobic coverage, as it was in the adult trials. Dosing of CAZ-AVI was determined based on previous PK studies. The study was single-blind due to the differences in fluid loads between the two regimens. Patients could remain on the IV medication up to day 15, or they could be changed to oral therapy starting on day 4 if determined by the investigator to have sufficient improvement. Table 49 describes how many patients were randomized and how many did or did not complete each part of the study. 86 patients were recruited and 83 were randomized into treatment groups and received IV study drug.

Table 49: Patient disposition for study D4280C00015

	CAZ-AVI + MTZ ***N=61***	***Meropenem*** ***N=22***	***Total*** ***N=83***

	N (%)	***N (%)***	***N (%)***
Patients randomized	61 (100)	22 (100)	83 (100)
Patients who received IV study drug	61 (100)	22 (100)	83 (100)
Patients who completed study up to TOC visit	59 (96.7)	22 (100)	81 (97.6)
Patients who completed study up to LFU visit	58 (95.1)	22 (100)	80 (96.4)
Patients who completed IV treatment	58 (95.1)	21 (95.5)	79 (95.2)
Patients who discontinued IV treatment	3 (4.9)	1 (4.5)	4 (4.8)
Patient/parent/legal representative decision	1 (1.6)	0	1 (1.2)
Lack of therapeutic response	1 (1.6)	0	1 (1.2)
Condition under investigation	0	1 (4.5)	1 (1.2)
Other	1 (1.6)	0	1 (1.2)
Patient who completed the study	59 (96.7)	22 (100)	81 (97.6)
Patients prematurely withdrawn from study	2 (3.3)	0	2 (2.4)
Parent/guardian decision	1 (1.6)	0	1 (1.2)
Investigator determination	1 (1.6)	0	1 (1.2)

Source: adapted from sponsor table 1.1.7.1.1.2-1 module 2.

cUTI

Patients were eligible for this study if they were aged ≥ 3 months to < 18 years and had cUTI clinically suspected and/or documented by culture, or acute pyelonephritis requiring hospitalization and treatment with IV antibiotics. Pyelonephritis was the most common underlying diagnosis (83.2% of patients had acute pyelonephritis). Only 15.8% of all patients had an underlying urological abnormality. They were stratified into four age cohorts: 12-18 years, 6-<12 years, 2-<6 years, and 3 months-<2 years (further divided into 1-<2 years and 3 months-<1 year). Patients received either CAZ-AVI or cefepime. Dosing of CAZ-AVI was determined based on previous PK studies. Dosing of cefepime was at the discretion of the investigator but could not exceed 2g/dose. The study was single-blind due to the differences in fluid loads between the two regimens. Patients could be switched to oral antibiotics starting on day 4 based on investigator discretion, or they could continue IV CAZ-AVI or IV cefepime up to day 14. Table 50 describes how many patients were randomized and how many did or did not complete each part of the study. There were 101 patients recruited and 97 were randomized to treatment groups; 95 received IV study drug.

Table 50: Patient disposition for study D4280C00016

	CAZ AVI N =68	***Cefepime N=29***	***Total N=97***
	N (%)	***N (%)***	***N (%)***
Patients randomized	68 (100)	29 (100)	97 (100)
Patients who received IV study drug	67 (98.5)	28 (96.6)	95 (97.9)

Patients who completed study up to TOC visit	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed study up to LFU visit	64 (94.1)	26 (89.7)	90 (92.8)
Patients who completed IV treatment	63 (92.6)	25 (86.2)	88 (90.7)
Patients who discontinued IV treatment	4 (5.9)	3 (10.3)	7 (7.2)
Patient/parent/legal representative decision	1 (1.5)	0	1 (1.0)
Adverse event	3 (4.4)	0	3 (3.1)
Condition under investigation	0	1 (3.4)	1 (1.0)
Based on enrollment culture of susceptibility results	0	2 (6.9)	2 (2.1)
Patient who completed the study	64 (94.1)	26 (89.7)	90 (92.8)
Patients prematurely withdrawn from study	4 (5.9)	3 (10.3)	7 (7.2)
Parent/guardian decision	2 (2.9)	0	2 (2.1)
Lack of therapeutic response	0	1 (3.4)	1 (1.0)
Patient lost to follow-up	1 (1.5)	1 (3.4)	2 (2.1)
Other	1 (1.5)	1 (3.4)	2 (2.1)

Source: adapted from sponsor table 1.1.7.1.3.2-1 module 2.

Adequacy of the safety database:

cIAI and cUTI

The safety database was adequate in terms of size and population in question. Safety evaluations included vital signs, ECGs, and routine physical examination and laboratory tests. Patients were monitored for adverse events including cephalosporin class effects. Adverse events of special interest (liver disorder, diarrhea, hypersensitivity/anaphylaxis, hematological disorder, and renal disorder) were identified and recorded.

9.1.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no issues identified with the integrity or quality of the data for either study. The data were submitted in standardized formats for review.

Categorization of Adverse Events

cIAI

Table 51 displays the categorization of adverse events (AEs). There were 32 total AEs in the CAZ-AVI + MTZ group (52.5% of patients) and 13 total AEs in the meropenem group (59.1% of patients). There were no AEs leading to death or discontinuation of study drug. There were 5 serious AEs in the CAZ-AVI + MTZ group (8.2%) and 1 SAE in the meropenem group (4.5%). Most AEs were defined as mild, but there were 4 severe AEs in the CAZ-AVI + MTZ group (6.6%) and 1

severe AE in the meropenem group (4.5%). There were 4 patients with AEs that fell into one of the special interest categories (liver disorder, diarrhea, hypersensitivity/anaphylaxis, hematological disorder, and renal disorder) in the CAZ-AVI + MTZ group (6.6%) and 4 in the Meropenem group (18.2%). Based on assessments by a blinded observer, only 1 AE was determined to be related to the study drug in the CAZ-AVI + MTZ group (1.6%) and 2 in the meropenem group (9.1%).

Table 51: Categorization of adverse events for study D4280C00015

Adverse event category	**CAZ-AVI + MTZ (N = 61)**	**MER (N = 22)**
	n (%)	n (%)
Any AE	32 (52.5)	13 (59.1)
Any AE with outcome leading to death	0	0
Any SAE	5 (8.2)	1 (4.5)
Any AE leading to discontinuation of study treatment	0	0
Any AE with severe intensity	4 (6.6)	1 (4.5)
Any AE of special interest	4 (6.6)	4 (18.2)
Any AE related to study IV treatment	1 (1.6)	2 (9.1)

Source: Adapted from Table 34 from D4280C00015 Clinical Study Report.

cUTI

Table 52 displays the categorization of AEs. There were 36 total AEs in the CAZ-AVI group (53.7%) and 15 total AEs in the cefepime group (53.6%). There were no AEs with outcomes leading to death in either group. There were 8 serious AEs in the CAZ-AVI group (11.9%) and 2 serious AEs in the cefepime group (7.1%). There were 3 AEs that led to discontinuation of CAZ-AVI (4.5%) and no AEs that led to discontinuation of cefepime. Most AEs were defined as mild but there were 6 determined to be severe in the CAZ-AVI group (9.0%) and 2 in the cefepime group (7.1%). There were 10 AEs that fell into a special interest category in the CAZ-AVI group (14.9%) and 4 in the cefepime group (14.3%). Based on decisions made by a blinded observer, 7 AEs were determined to be related to the study drug in the CAZ-AVI group (10.4%) and 1 in the cefepime group (1.0%).

Table 52: Categorization of adverse events for study D4280C00016

Adverse event category	**CAZ-AVI (N = 67)**	**CEF (N=28)**
	n (%)	n (%)
Any AE	36 (53.7)	15 (53.6)
Any AE with outcome leading to death	0	0
Any SAE	8 (11.9)	2 (7.1)

Any AE leading to discontinuation of study treatment	3 (4.5)	0
Any AE with severe intensity	6 (9.0)	2 (7.1)
Any AE of special interest	10 (14.9)	4 (14.3)
Any AE related to study IV treatment	7 (10.4)	1 (3.6)

Source: table adapted from sponsor table 33 from D4280C00016 Clinical Study Report

Routine Clinical Tests

cIAI

Routine clinical tests done at baseline at specified time points included EKG, CBC with differential, chemistry panel, CrCl calculation (using bedside Schwartz formula), ESR, CRP (optional), urine or serum pregnancy test in female patients of child-bearing age, urinalysis, and intra-abdominal fluid sample. The intra-abdominal fluid sample was done at baseline (during the patient's surgical procedure) and only repeated if clinically indicated. Direct Coombs test was done at baseline and repeated at a later visit. The investigators set a 2.4 cc/kg maximum limit on blood volume taken from patients throughout the course of the study. Complete physical exam including height, weight and BMI measurements was done. One set of vital signs including pulse, blood pressure, body temperature and respiratory rate were recorded at each visit.

cUTI

Routine clinical tests done at baseline and at specified time points included EKG, CBC with differential, chemistry panel, CrCl calculation (using bedside Schwartz formula), ESR, CRP (optional), urine or serum pregnancy test in female patients of child-bearing age, urinalysis, and urine culture. Blood culture was performed when clinically indicated. Direct Coombs test was done at baseline and repeated at a later visit. The investigators set a 2.4cc/kg maximum limit on blood volume taken from patients throughout the course of the study. Complete physical exam including height, weight and BMI measurements were done. One set of vital signs including pulse, blood pressure, body temperature and respiratory rate were recorded at each visit.

9.1.4. Safety Results

Deaths

There were no deaths reported in either study.

Serious Adverse Events

cIAI

There were 6 serious adverse events in total with 5 in the CAZ-AVI + metronidazole group and 1 in the meropenem group (summarized in Table 53, below). The patients in the CAZ-AVI + metronidazole group will be described here.

Patient (b) (6) was a 15-year-old male from the Czech Republic. He experienced right renal colic on study day 14 (7 days after the last dose of study drug) which led to hospitalization. During this event he was treated with methimazole sodium, hyoscine butylbromide, paracetamol, domperidone, furosemide, thiethylperazine maleate, and plasmalyte infusion. The event was resolved on study day 17.

Reviewer comment: Nephrolithiasis was reported as an adverse event of <1% of adult patients in phase 3 trials for CAZ-AVI and was added to the drug label previously.

Patient (b) (6) was a 12-year-old female from Taiwan who experienced postoperative ileus on study day 14 (7 days after the last dose of study drug) which led to hospitalization. She was treated with gentamicin, metronidazole, cefazolin, simethicone, ciprofloxacin, potassium chloride, ketorolac, cetirizine, hexachlorophene, chlorphenamine maleate, and menthol. The investigators attributed this event to use of cefadroxil. The event was resolved on study day 28.

Reviewer comment: This patient's ileus could have been secondary to many factors such as the surgical procedure itself, electrolyte abnormalities or pain medications. The role of CAZ-AVI in the event, however, cannot be excluded.

Patient (b) (6) was a 7-year-old male from Hungary who experienced stricture of the urethral meatus on study day 23 (15 days after the last dose of study drug) and voiding difficulties which led to hospitalization. He had previously been reported to have mucosal ulceration of the urethral meatus starting on study day 3. The AE was said to be resolved also on study day 23 and he was discharged from the hospital.

Reviewer comment: The treatment for the patient's stricture was not further described. He may have had urinary catheterization during his initial surgical procedure which could have caused the ulceration, voiding difficulty and stricture. The role of CAZ-AVI in the event, however, cannot be excluded.

Patient (b) (6) was a 10-year-old female from Turkey who experienced severe ileus and large intestine perforation, which prolonged the hospital stay. The event is said to have occurred and resolved on study day 5 (also day 5 of study drug) and she was discharged on study day 10. No changes were made to study drug.

Reviewer comment: Treatment of the ileus and perforation was not well described; however, these events were most likely related to the patient's underlying disease process and/or surgical intervention. As above, the possible contribution of CAZ-AVI to the event cannot be excluded.

Patient (b) (6) was a 4-year-old male from Spain who experienced intestinal obstruction on study day 9 (also day 9 of study drug). No changes were made to study drug. He was treated with dexamethasone, fentanyl, propofol, rocuronium bromide, and tramadol. The event was considered resolved on study day 17.

Reviewer comment: This event was most likely related to the underlying disease process and/or surgical intervention, but the role of CAZ-AVI cannot be excluded.

Table 53: Serious Adverse Events in Study D4280C00015

System Organ Class/ MedDRA Preferred Term	**CAZ-AVI + MTZ (N = 61)**	**MER (N = 22)**
	n(%)	n(%)
Patients with any SAE	5 (8.2)	1 (4.5)
Gastrointestinal disorders	2 (3.3)	1 (4.5)
Ileus	1 (1.6)	1 (4.5)
Intestinal obstruction	1 (1.6)	0
Large intestine perforation	1 (1.6)	0
Injury, poisoning and procedural complications	1 (1.6)	0
Postoperative ileus	1 (1.6)	0
Renal and urinary disorders	2 (3.3)	0
Renal colic	1 (1.6)	0
Urethral meatus stenosis	1 (1.6)	0

Source: adapted from sponsor table 38 in D4280C00015 Clinical Study Report

cUTI

There were 10 serious adverse events in total, with 8 in the CAZ-AVI group and 2 in the cefepime group (see Table 54). The patients in the CAZ-AVI group will be described below. The 2 patients in the cefepime group had SAEs of cystitis and pyelonephritis.

Patient (b) (6) was a 16-year-old female from Turkey who experienced neurological symptoms of the lower extremities leading to discontinuation of the drug (see Dropouts and/or Discontinuations Due to Adverse Effects section for full description and comments).

Patient (b) (6) was a 17-year-old female from the United States who experienced abdominal pain, constipation and nephrolithiasis on study day 26 in the setting of a previous history of constipation and nephrolithiasis. She had already discontinued the drug on day 2 due to dizziness, nausea and vomiting (see Dropouts and/or Discontinuations Due to Adverse Effects section for full description and comments).

Patient (b) (6) was a 3-year-old female from the Czech Republic who developed a severe viral infection on study day 35 (32 days after last dose of study drug) leading to hospitalization.

She was treated with ibuprofen, calcium, vitamins NOS, sodium chloride, nasal preparations and ambroxol hydrochloride. The event was resolved on day 41.

Reviewer comment: This SAE occurred over a month after the study drug finished. More importantly, viral infection is very common in children and is likely to be incidental.

Patient (b) (6) was a 6-year-old male from Taiwan who developed a UTI on study day 27 (19 days after stopping study drug) leading to hospitalization. His baseline pathogen was *E. coli* and his culture at the TOC visit grew *E. faecalis*. The event was resolved on study day 38 after treatment with several antibiotics including amikacin, cefepime, and ampicillin. He was discharged with ampicillin prophylaxis. This patient had a history of reflux nephropathy, vesicoureteral reflux, neurogenic bladder and UTIs.

Patient (b) (6) was a 4-year-old female from Taiwan who developed a UTI on day 20 (16 days after stopping study drug) leading to hospitalization. The patient had a past medical history of congenital megaureter, UTI and hydronephrosis. Her initial infection was caused by *K. pneumoniae*, which cleared on subsequent cultures, but culture during the AE grew the same organism. The event was resolved on day 38 after treatment including ceftriaxone, amoxicillin and clavulanic acid, cefazolin and ofloxacin.

Patient (b) (6) was a 5-month-old female from the Czech Republic who developed acute pyelonephritis on study day 45 (40 days after stopping study drug) leading to hospitalization. There was no reported past medical history of underlying urological issues. Her initial infection was caused by *E. coli*, which cleared in all cultures done later in the study. There is no further detail about the microbiological cause of the acute pyelonephritis. The event was resolved on study day 56 after treatment with amoxicillin and clavulanic acid.

Patient (b) (6) was a 6-month-old female from the Czech Republic who developed acute pyelonephritis on study day 39 (34 days after stopping study drug) leading to hospitalization. The pathogen at baseline was *E. coli*, which had cleared in subsequent cultures but was again isolated on day 40. There was no reported past medical history of underlying urological issues. The event was resolved on day 49 after treatment with cefuroxime.

Patient (b) (6) was a 4-month-old female from Taiwan who developed a UTI on day 38 (35 days after stopping study drug) leading to hospitalization. Baseline pathogen was *E. coli* which cleared on subsequent cultures, and it is unclear from the documentation whether the pathogen causing repeat UTI was the same. This patient had a past medical history of persistent UTIs, hydronephrosis, hydroureter, and vesicoureteral reflux. The event was resolved on day 65 after treatment with sulfamethoxazole + trimethoprim and cefixime.

Reviewer comment: Cases of UTI and pyelonephritis following the study may represent either treatment failures or new infections, rather than AEs. In these cases of repeated UTIs following the study, some of the patients had reported history of underlying urological issues that would

predispose them to frequent UTI/cUTI. There were no persistent organisms with increasing MICs indicating resistance. The events were all resolved following hospitalization and treatment with different antibiotics.

Table 54: Serious Adverse Events in Study D4280C00016

System Organ Class/ MedDRA Preferred Term	CAZ-AVI (N=67)	CEF (N=28)
	N (%)	N (%)
Patients with any SAE	8 (11.9)	2 (7.1)
Gastrointestinal disorders	**1 (1.5)**	**0**
Abdominal pain	1 (1.5)	0
Constipation	1 (1.5)	0
Infections and infestations	**6 (9.0)**	**2 (7.1)**
Cystitis	0	1 (3.6)
Pyelonephritis acute	2 (3.0)	1 (3.6)
Urinary tract infection	3 (4.5)	0
Viral infection	1 (1.5)	0
Nervous system disorders	**1 (1.5)**	**0**
Nervous system disorder	1 (1.5)	0
Renal and urinary disorders	**1 (1.5)**	**0**
Nephrolithiasis	1 (1.5)	0

Source: adapted from sponsor table 37 in D4280C00016 Clinical Study Report

Dropouts and/or Discontinuations Due to Adverse Effects

cIAI

There were no discontinuations of study drug due to AEs reported in this study.

cUTI

There were 3 patients in the CAZ-AVI group who discontinued the study drug due to an AE.

Patient (b) (6) was a 16-year-old female from Turkey with a complicated lower tract UTI. CAZ-AVI was discontinued on study day 3 due to a "severe nervous system disorder." On study day 3, she suddenly developed inability to walk and had loss of strength, pins and needles and tingling of both legs. She could not move legs on command during physical examination. The event was determined to be resolved on the same day that it occurred (study day 3) without any residual neurological changes. The patient recovered from this event without treatment. Of note, her past medical history prior to the study lists strength loss, sensation loss, muscle

weakness, tingling in her feet and hands, depression and anxiety. The investigator thought that the AE was possibly due to study drug.

Reviewer comment: The role of CAZ-AVI cannot be ruled out, but this event seems less likely to be caused by the study drug due to the nonspecific nature of the symptoms and the fact that they resolved without treatment. The symptoms also seem to be consistent with pre-existing complaints that the patient had before entering the study, such as muscle weakness and anxiety.

Patient (b) (6) was a 17-year-old female from the United States with acute pyelonephritis. She reported moderate dizziness, nausea and vomiting on study day 2 of the drug and the drug was discontinued. The symptoms were resolved by study day 3 without treatment. On day 26 the patient also experienced abdominal pain, kidney stones and constipation which resolved on day 34. The patient was being treated with microgestin, zofran, metformin, escitalopram, naproxen, miralax, potassium citrate, paracetamol, diphenhydramine, ketorolac, morphine, senna, and glycerin suppository. These later symptoms were not thought to be associated with study drug. The patient's past medical history included chronic constipation and kidney stones.

Reviewer comment: The dizziness, nausea and vomiting could have been due to the patient's disease process, but the fact that they resolved without treatment once the drug was discontinued points towards the drug as a potential cause. Dizziness, nausea and vomiting are known to be common adverse effects of CAZ-AVI and are already reported on the drug label. It is less likely that the drug caused the later symptoms of constipation and kidney stones due to the time course and her pre-existing diagnoses of constipation and kidney stones, but the role of CAZ-AVI cannot be excluded, especially because nephrolithiasis was a new safety signal noted in the review of adult trials. She had an underlying predisposition to nephrolithiasis that could have possibly been exacerbated by the drug. She was also taking morphine as needed which might have worsened her constipation.

Patient (b) (6) was a 6-year-old female from Turkey with acute pyelonephritis. She only received one dose of study drug which was discontinued on study day 1 due to tachycardia. Her heart rate prior to the infusion was 108 bpm and her heart rate increased to 140 bpm after the infusion. Her blood pressure remained stable and her physical exam was benign except for tachycardia. The event was considered resolved on study day 3. At subsequent study visits her recorded heart rates ranged from 88-117 bpm. The investigator determined that the AE was not related to the drug.

Reviewer comment: It is difficult to determine causality based on increase in heart rate after just one infusion, and she could have had many other factors leading to tachycardia including fever, agitation, pain, dehydration, or the infection itself. There were no reports of other vital sign changes or physical exam changes to indicate a possible allergic or anaphylactic reaction to the drug.

No patients in the cefepime group had an AE that led to discontinuation of study drug.

Significant Adverse Events

cIAI

Known cephalosporin class effects including liver disorders, diarrhea, hypersensitivity reactions, hematological disorders, and renal disorders were deemed AEs of special interest (AESI). There were 4 patients in each group with AESIs (see Table 55). No patients in either group were reported to have liver or renal disorders.

One patient (1.6%) in the CAZ-AVI + metronidazole group (Patient (b) (6) was a 6-year-old male from Greece who had diarrhea on study day 3 and was treated with IV fluids and resolved on the same day without changing the study drug. The same patient also experienced dizziness on day 5 which resolved without treatment on the same day.

One patient in the CAZ-AVI + metronidazole group (1.6%) and 2 in the meropenem group had cough (9.1%). The patient in the CAZ-AVI group (Patient (b) (6) was a 13-year-old male from the Czech Republic who had a mild cough starting on day 7 which was treated with cough medicine (Stoptussin), and the study drug was continued. The study drug was stopped on study day 9 and the cough resolved on study day 11.

Reviewer comment: The role of CAZ-AVI cannot be excluded based on the time course of the cough in relation to IV drug, but this was the only patient in the study with cough. In addition, hospitalized patients have many reasons to develop cough including atelectasis and nosocomial infection.

One patient (1.6%) in the CAZ-AVI + metronidazole group (Patient (b) (6) an 11-year-old female from Taiwan, had pruritus which started on day 31 (23 days after stopping study drug) and was said to be associated with insects.

One patient in the CAZ-AVI + metronidazole group (1.6%) and one patient in the meropenem group (4.5%) had a rash. The patient in the CAZ-AVI group (Patient (b) (6) was a 6-year-old male from Taiwan. He had a mild rash (location not specified) starting on study day 2 that was treated with an antihistamine and lotion, and study drug was continued. The patient was switched to an oral antibiotic on study day 9 and the rash resolved on study day 10.
One patient in the meropenem group had anemia (4.5%). Although not included in the investigator's AESI list, one patient in each group had a negative Coombs test at baseline which was later positive.

Reviewer comment: Coombs seroconversion is a known effect of cephalosporins, but there were no reports of symptomatic hemolytic anemia associated with Coombs seroconversion in either study.

Most broad-spectrum antibiotics including cephalosporins have also been associated with *C. difficile* infection, but no patients in this study were reported to have C. difficile.
There are warnings on labels of other cephalosporins that seizures may result from overdose in patients with renal impairment, but there were no seizures reported in this study.

Reviewer comment: The patients with rash, cough and pruritus could have possibly had hypersensitivity reactions, which is less likely due to timing of AEs and other circumstances, but they did not exhibit anaphylaxis because there were no other body systems involved and no vital sign changes described.

Table 55: Adverse Events of Special Interest in Study D4280C00015

Safety Topic/MedDRA Preferred Term	**CAZ-AVI + MTZ (N = 61)**	**MER (N = 22)**
Patients with at least 1 AE of special interest	4 (6.6)	4 (18.2)
Liver Disorders	0	0
Diarrhea	1 (1.6)	0
Hypersensitivity/Anaphylaxis	3 (4.9)	3 (13.6)
Cough	1 (1.6)	2 (9.1)
Pruritus	1 (1.6)	0
Rash	1 (1.6)	1 (4.5)
Hematological Disorders	0	1 (4.5)
Anemia	0	1 (4.5)
Renal Disorders	0	0

Source: adapted from sponsor table 37 in D4280C00015 Clinical Study Report

cUTI

Known cephalosporin class effects, including liver disorders, diarrhea, hypersensitivity reactions, hematological disorders, and renal disorders were deemed AEs of special interest (AESI). There were 10 patients in the CAZ-AVI group with an AESI and 4 patients in the cefepime group with an AESI (see Table 56). No patients were reported to have hematological disorders or renal disorders. There were 2 patients from each treatment group who initially had a negative Coombs test that later turned positive, but they did not have symptomatic hemolytic anemia.
There was one patient (1.5%) in the CAZ-AVI group (Patient [redacted] (b) (6) with a liver disorder (increased GGT). This patient was a 16-year-old female from the Czech Republic who had ALP, AST, ALT and LDH within normal range and GGT at the upper limit of normal (0.40 μkat/L [NR: 0.07-0.4 μkat/L]) at the baseline visit. On study day 4, the GGT increased to 0.86 μkat/L but all other labs remained normal. The patient was changed to oral antibiotics on study day 4 as well, but they state that no action was taken on the study drug due to the AE. The patient's GGT began to trend down without treatment and resolved on study day 33. There were no patients in the cefepime group with a liver disorder.

Reviewer comment: The patient's GGT was already slightly elevated at the beginning of the study and then increased after 4 days of study drug; it may have been trending up

independently, but the role of CAZ-AVI cannot be excluded, especially because the GGT decreased when the patient was changed to an oral antibiotic. The initial increase and later decrease could have also been related to the disease process. It is reassuring that all other labs, including AST and ALT, remained normal.

There were 5 patients with diarrhea in the CAZ-AVI group (7.5%). Patient (b) (6) was a 3-month-old male from the Czech Republic who developed diarrhea on study day 4. No changes were made to the study drug. He was treated with Hylak (a probiotic) and the diarrhea resolved on study day 11. Patient (b) (6) was a 2-year-old female from the Czech Republic who developed diarrhea on study day 6. She had been switched to oral antibiotics 2 days prior to development of diarrhea. She was treated with Biopron (a probiotic) and *Lactobacillus* and her diarrhea resolved on study day 8. Patient (b) (6) was a 7-month-old female from the Czech Republic who developed diarrhea on study day 13 (8 days after switching to oral antibiotics) She was treated with *Bifidobacterium* spp/*Lactobacillus* spp capsules and the diarrhea resolved on study day 18. Patient (b) (6) was an 11-month-old female from the Czech Republic who developed diarrhea on study day 6 (which was 2 days after switching to oral antibiotics). She did not receive any treatment and the diarrhea resolved on study day 7. Patient (b) (6) was a 1-year-old female from Greece who developed diarrhea on study day 2, which resolved within 4 hours without intervention or change in study drug. There were 3 patients in the cefepime group with diarrhea (10.7%).

There were 2 patients with cough in the CAZ-AVI group (3.0%). Patient (b) (6) was a 10-month-old female from Hungary who developed cough on study day 28 (21 days after stopping study drug). The cough was treated with Sinupret (an herbal supplement), amoxicillin and theophylline and the cough resolved on study day 32. Patient (b) (6) was a 4-month-old female from Taiwan who developed cough on study day 5, which was the day after the last dose of IV drug. Her cough was treated with cyproheptadine and resolved on day 11; later, on study day 40 the cough returned, but resolved the next day without treatment. There was 1 patient in the cefepime group with cough (3.6%).

No patients in the CAZ-AVI group experienced pruritus but 1 patient in the cefepime group did (3.6%).

There were 3 patients in the CAZ-AVI group with rash (4.5%). Patient (b) (6) was an 8-year-old female from Poland who developed rash on her face and neck on study day 3, which resolved in 20 minutes without intervention. She then developed rash on her right leg on study day 5 which resolved in 75 minutes without intervention. No changes were made to study drug. It was not specified whether the rashes occurred at a certain time in relation to administration of study drug. Patient (b) (6) was a 2-year-old female from the Czech Republic who developed a rash on day 11, which was 7 days after last dose of study drug. She was treated with Zyrtec and the rash was reported to be resolved on day 47; this patient also developed diarrhea on day 6 (see above). Patient (b) (6) was a 3-year-old female from Turkey who developed a rash on study day 2. There was an interruption in study drug due to the rash, but

the patient continued IV drug and was switched to PO drug on day 6. The rash was treated with pheniramine and dexamethasone and resolved on day 3. There were 2 patients in the cefepime group with rash (7.1%).

Reviewer comment: The patients with rash and cough could have possibly had hypersensitivity reactions due to study drug, but they did not exhibit anaphylaxis because there were no other body systems involved and no vital sign changes described.

Other cephalosporins have also been associated with *C. difficile* infection, but no patients in this study were reported to have *C. difficile*.

There are warnings on labels of other cephalosporins that seizures may result from overdose in patients with renal impairment, but there were no seizures reported in this study.

Table 56: Adverse Events of Special Interest in Study D4280C00016

Safety Topic/MedDRA Preferred Term	**CAZ-AVI (N = 67) n (%)**	**CEF (N = 28) n (%)**
Patients with at least 1 AE of special interest	10 (14.9)	4 (14.3)
Liver Disorders	1 (1.5)	0
Gamma-glutamyltransferase increased	1 (1.5)	0
Diarrhea	5 (7.5)	3 (10.7)
Hypersensitivity/Anaphylaxis	5 (7.5)	2 (7.1)
Cough	2 (3.0)	1 (3.6)
Pruritus	0	1 (3.6)
Rash	3 (4.5)	2 (7.1)
Hematological Disorders	0	0
Renal Disorders	0	0

Source: adapted from sponsor table 36 from D4280C00016 Clinical Study Report.

Treatment Emergent Adverse Events and Adverse Reactions

cIAI

There were no deaths, dose modifications or discontinuations due to AEs, and the most serious and significant adverse events are described above. The most common AEs were gastrointestinal disorders and infusion site reactions (see Table 57). Vomiting occurred in 9 patients in the CAZ-AVI + metronidazole group (14.8%) and 2 patients in the meropenem group (9.1%). Infusion site phlebitis occurred in 4 patients in the CAZ-AVI + metronidazole group (6.6%) and no patients in the meropenem group. Table 9 displays additional AEs that were seen in at least 2 patients.

Reviewer comment: vomiting and infusion site phlebitis are expected AEs for both cephalosporins and metronidazole. Vomiting could also have been secondary to the underlying condition of intra-abdominal infection.

Adverse events that the investigator labeled as "severe" included ileus, intestinal obstruction, large intestinal perforation, renal colic and vomiting. These occurred in only 1 patient each in the CAZ-AVI + metronidazole group and narratives are provided and discussed in above sections. One patient in the meropenem group had a severe ileus and no other severe AEs were reported in the meropenem group.

Table 57: Adverse Events Occurring in ≥2 Patients in Study D4280C00015

System Organ Class/ MedDRA Preferred Term	CAZ-AVI + MTZ (N = 61)	MER (N = 22)
Patients with any AE	32 (52.5)	13 (59.1)
Gastrointestinal disorders	**13 (21.3)**	**6 (27.3)**
Abdominal pain	0	2 (9.1)
Vomiting	9 (14.8)	2 (9.1)
General disorders and administration site conditions	**8 (13.1)**	**0**
Infusion site phlebitis	4 (6.6)	0
Pyrexia	2 (3.3)	0
Infections and infestations	**9 (14.8)**	**3 (13.6)**
Respiratory tract infection viral	2 (3.3)	0
Injury, poisoning and procedural complications	**5 (8.2)**	**1 (4.5)**
Seroma	3 (4.9)	0
Metabolism and nutrition disorders	**3 (4.9)**	**0**
Hypokalemia	2 (3.3)	0
Respiratory, thoracic and mediastinal disorders	**2 (3.3)**	**2 (9.1)**
Cough	1 (1.6)	2 (9.1)

Source: adapted from sponsor table 35 in D4280C00015 Clinical Study Report

cUTI

There were no deaths or dose adjustments due to AEs, and the most serious and significant AEs and reasons for discontinuation are discussed above. The most common AEs in the CAZ-AVI group were diarrhea (7.5%) and UTI (7.5%) (see Table 58).

Reviewer comment: Diarrhea is an expected AE for cephalosporins, but it is important to note that there were no cases of C. difficile reported. The UTIs are not seen as AEs by the reviewer, rather as possible treatment failures or emergent infections due to the patient's history of urological abnormalities.

Other adverse events that were labeled "severe" by the investigator included abdominal pain, constipation, nephrolithiasis, nervous system disorder, pyelonephritis, tachycardia, and viral infection. In the CAZ-AVI group, these all occurred in only 1 patient except for pyelonephritis which occurred in 2 patients. The narratives for these severe adverse events are provided and

discussed in above sections. There were only 2 severe AEs in the cefepime group, one case of cystitis and one case of pyelonephritis.

Table 58: Adverse Events Occurring in ≥2 Patients in Study D4280C00016

System Organ Class/ MedDRA Preferred Term	CAZ-AVI (N = 67) n (%)	CEF (N = 28) n (%)
Patients with any AE	36 (53.7)	14 (50.0)
Gastrointestinal disorders	**9 (13.4)**	**6 (21.4)**
Abdominal pain	2 (3.0)	0
Diarrhea	5 (7.5)	3 (10.7)
Nausea	2 (3.0)	1 (3.6)
Vomiting	2 (3.0)	2 (7.1)
General disorders and administration site conditions	**3 (4.5)**	**2 (7.1)**
Pyrexia	2 (3.0)	1 (3.6)
Infections and infestations	**21 (31.3)**	**5 (17.9)**
Gastroenteritis	2 (3.0)	0
Nasopharyngitis	2 (3.0)	0
Pyelonephritis acute	2 (3.0)	1 (3.6)
Rhinitis	4 (6.0)	2 (7.1)
Upper respiratory tract infection	3 (4.5)	0
Urinary tract infection	5 (7.5)	0
Viral upper respiratory tract infection	2 (3.0)	0
Vulvitis	2 (3.0)	0
Respiratory, thoracic and mediastinal disorders	**3 (4.5)**	**1 (3.6)**
Cough	2 (3.0)	1 (3.6)
Skin and subcutaneous tissue disorders	**7 (10.4)**	**4 (14.3)**
Intertrigo	1 (1.5)	2 (7.1)
Rash	3 (4.5)	2 (7.1)

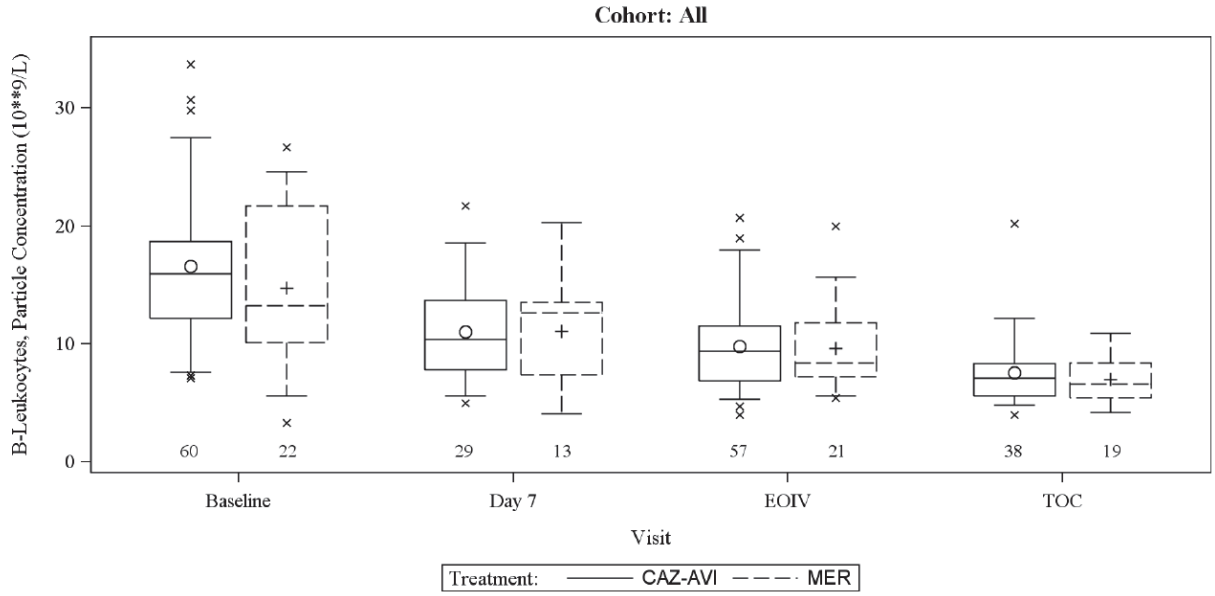
Source: adapted from sponsor table 34 from D4280C00016 Clinical Study Report

Laboratory Findings

cIAI

Leukocytes were slightly elevated initially and decreased over time (within normal range) for all cohorts below figure 2) (REF _Ref2869281 \h). Neutrophil percentage decreased and lymphocyte percentage increased over time. Platelets initially increased then later decreased. CRP decreased throughout the study. No cases met Hy's Law criteria. There was only 1 patient with ALT > 3x the upper limit of normal (ULN). There was 1 patient with AST >3x normal. No patients had bilirubin >2x ULN. One patient had alkaline phosphatase >2x ULN. There was 1 patient with elevated GGT who is discussed in the "Significant Adverse Events" section above. There was one patient per treatment group who initially had a negative Coombs test that later turned positive but did not have symptomatic hemolytic anemia.

Figure 5: Trend in Leukocytes for All Cohorts in Study D4280C00015

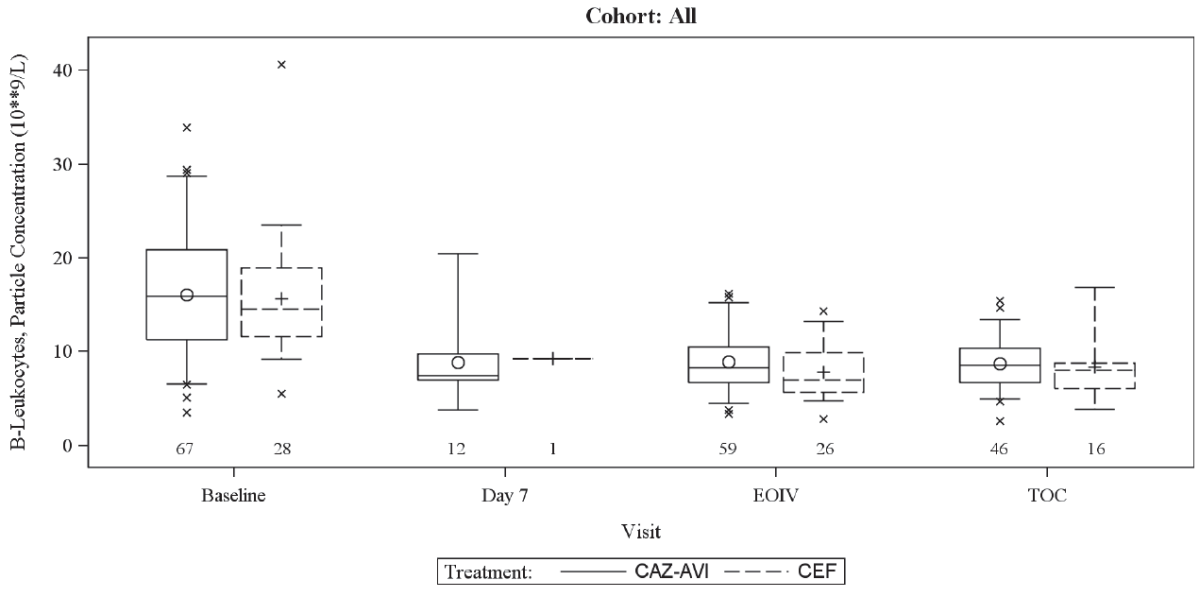


Source: Sponsor table 14.3.4.1.4.5 from D4280C00015 Clinical Study Report

cUTI

Leukocytes decreased over time (within normal range) for all cohorts (Figure 6). Neutrophil percentage decreased and lymphocyte percentage increased over time. Platelets initially increased then decreased. CRP decreased throughout the study. No cases met Hy's Law criteria. There were no patients with AST or ALT >3x ULN. There were no patients with bilirubin >2x ULN. There were 2 patients with alkaline phosphatase >2x ULN. There were 2 patients per treatment group who initially had a negative Coombs test that later turned positive, but they did not have symptomatic hemolytic anemia.

Figure 6: Trend in Leukocytes for All Cohorts in Study D4280C00016



Source: Sponsor table 14.3.4.1.4.5 from D4280C00015 Clinical Study Report

Reviewer comments: Decreases in leukocytes, neutrophil percentage and CRP throughout the study are consistent with resolving infections. An increase in platelet count during the early stages of infection can be interpreted as an acute phase reactant, so the later decrease is expected as the infection subsides. There were no significant differences between treatment groups.

Coombs seroconversion has been seen previously with cephalosporins, including AVYCAZ, but importantly, none of the patients experienced hemolytic anemia.

An isolated elevation in alkaline phosphatase without other liver function abnormalities is reassuring. Alkaline phosphatase may be elevated in pediatric patients during periods of bone growth.

Vital Signs

Vital signs were analyzed separately for each cohort, which is appropriate given the variation in normal vital sign ranges between pediatric age groups. There was only one set of vital signs per study visit, and only while patients were still on IV treatment, which slightly limits the interpretation as that one set of vital signs may not have been representative of the patient's overall trend. Descriptive statistics were provided by the sponsor and show baseline vitals and change from baseline at each visit for each cohort.
There were no reported cardiac adverse events other than one discontinuation due to tachycardia, which is discussed above in the Discontinuations section. Review of temperature, heart rate, respiratory rate and systolic and diastolic blood pressures in all cohorts did not

reveal clinically significant changes throughout treatment.

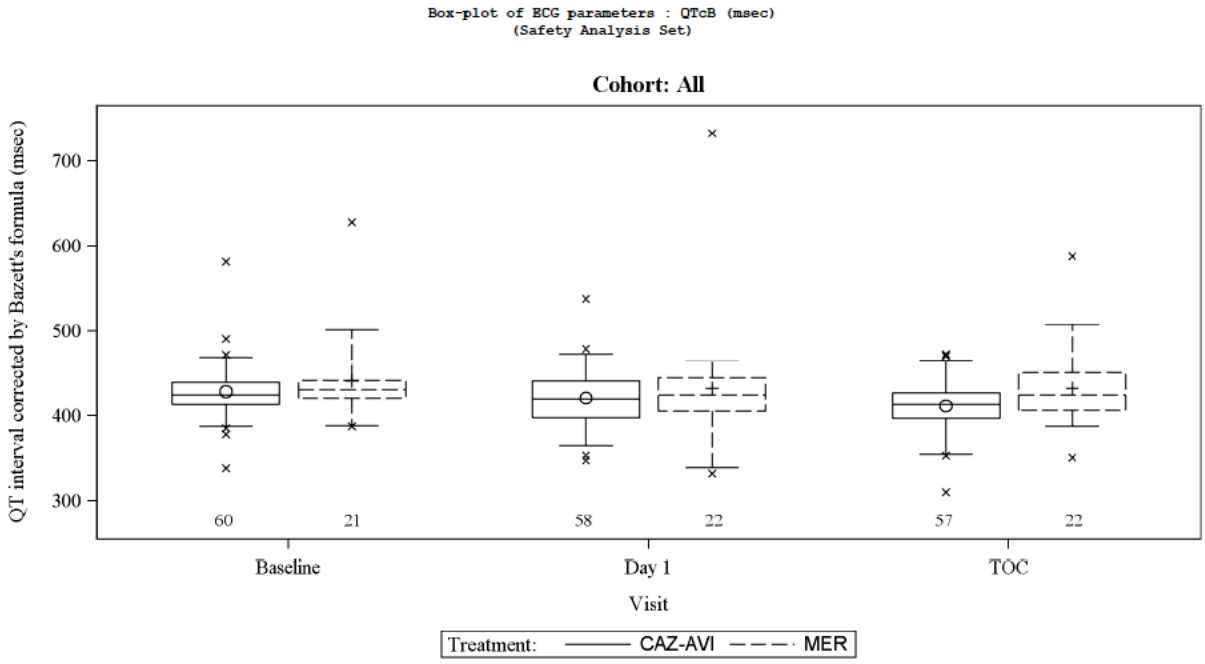
Electrocardiograms (ECGs)

In both studies, ECGs were done at baseline, day 1 of study drug, and at Test of Cure (TOC) visit. The parameters recorded by the investigator were heart rate (beats/min), QRS duration (msec), RR duration (msec), PR duration (msec), and QT duration (msec).

QT Interval

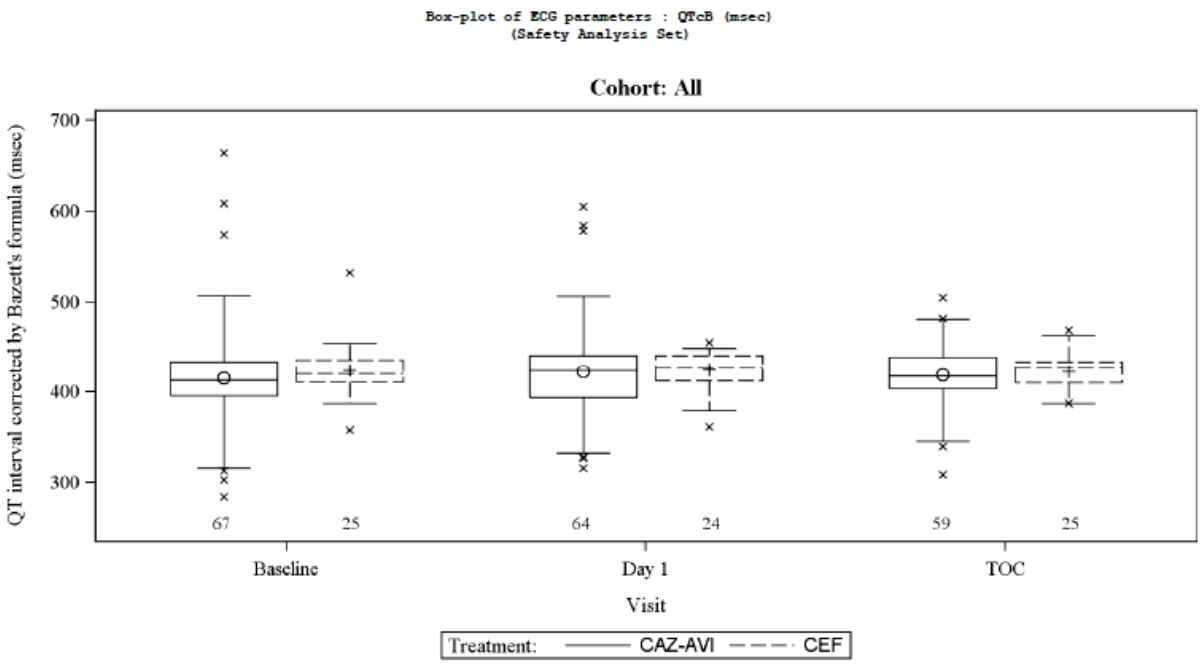
ECGs were done at baseline, on day 1 of study drug and at the TOC visit to compare intervals at baseline to later visits while on IV study drug. QT was corrected using two formulas (QTcB from Bazett's formula and QTcF from Fridericia's formula). Figure 7 displays box plots of the QTcB for all cohorts throughout the cIAI study and Figure 8 displays box plots of the QTcB for all cohorts in the cUTI study. The QTcF trend was similar. There were no clinically significant instances of prolonged QT, and most patients remained within normal limits for pediatric patients (<450msec). There were outliers as shown in the figures, but there was no report of symptomatic cardiac arrhythmia in either study.

Figure 7: QTcB measurements for all cohorts in study D4280C00015



Source: Figure 14.3.4.3.1.6 in D4280C00015 Clinical Study Report

Figure 8: QTcB measurements for all cohorts in study D4280C00016



Source: Figure 14.3.4.3.1.6 in D4280C00016 Clinical Study Report

Reviewer comment: AVYCAZ is not associated with QT segment prolongation in adult patients and is not expected to occur in pediatric patients.

Immunogenicity

There are no studies evaluating the immunogenicity of AVYCAZ.

9.1.5. Analysis of Submission-Specific Safety Issues

There were no cases of C. difficile associated diarrhea in either study. There were no cases of anaphylaxis in either study. Other cephalosporin class effects are discussed above in the Significant Adverse Events section. The most common adverse effect between the two studies was vomiting which occurred in 8.6% of patients treated with AVYCAZ compared to 8% of patients treated with comparators. This was the only adverse event occurring at a rate greater than 5%.

Reviewer comment: Vomiting is not a new safety signal for cephalosporins.

9.1.6. Safety Analyses by Demographic Subgroups

The number of patients in each study was very small, therefore no specific safety analyses were done by subgroup, but no obvious patterns emerged on review of the data. Limitations in the safety population are discussed below.

Of the patients in the cUTI study, 83.2% of patients had acute pyelonephritis; 15.8% of all patients had an underlying urological abnormality. Of the patients in the cIAI study, 86.7% of patients had appendiceal perforation or peri-appendiceal abscess, 10.8% had secondary peritonitis, 2.4% had traumatic intestinal perforation. Although pyelonephritis and appendicitis were by far the most common diagnoses in the cUTI and cIAI studies, respectively, it is the opinion of the reviewer that this does not significantly change the ability to interpret the study results.

Most of the patients were white, so it is not possible to comment on any potential differences in the safety profile of the drug in patients of other racial backgrounds.

Most of the patients were male (72.1%) in the cIAI study and the average age was 10.95 years. In the cUTI study, 83.6% of patients were female and the average age was 6.08 years.
Due to recruiting difficulties, no patients in Cohort 4 were randomized to CAZ-AVI in the cIAI study, but there were 26 patients in the cUTI study in Cohort 4 (mean age 11.4 months, ranging 3.5 months to 22.4 months). These numbers reflect the expected populations to get these infections; cUTI would be much more common in younger female patients. It is also understandable that there was a dearth of patients between age 3 months-2 years with cIAI. For example, necrotizing enterocolitis is a very common cause of intra-abdominal infection in much younger patients but would be rare after age 3 months. Appendicitis is common in school age children but rare under age 2 years. Although no cIAI patient in Cohort 4 was treated with CAZ-AVI, the safety profile would be unlikely to be different between cUTI and cIAI patients in Cohort 4.

There was only 1 patient between both trials randomized to the AVYCAZ arm with a CrCl between 30 and 50. It is difficult to come to any conclusions about safety based on only one patient, and if dosing recommendations are made based on pharmacological models, it would be helpful to collect post-marketing safety data on patients in this population.

9.1.7. Specific Safety Studies/Clinical Trials

The two studies under review for this supplement both had safety and tolerability as the primary objective, but no further safety studies were performed for the population in question.

9.1.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Previously, ceftazidime and avibactam were not found to have mutagenic potential in several in vivo and in vitro assays. There have been no safety signals related to human carcinogenicity. In general, antibacterial drugs are typically administered as a single course of treatment over a limited period of time for an acute illness; therefore, prolonged exposure is not anticipated.

Pediatrics and Assessment of Effects on Growth

The studies under review were both pediatric studies. The patients were not followed long-term to determine effects of the drug on growth, or other developmental parameters. This drug is not intended for long-term use.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

AVYCAZ and its components are not known to be associated with abuse, withdrawal or rebound effects. It is also administered in a hospital setting making the possibility of overdose less likely.

9.1.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

As of the cutoff date of February 24, 2018, there are 235 safety reports involving AVYCAZ since February 25, 2015. These are not specific to pediatric patients. The most frequently reported term was off-label use (38 cases). Other reported terms included “23 deaths, 14 cases of septic shock, 13 cases each of drug ineffective and drug resistance, 11 cases of nausea, 10 cases of treatment failure, 9 cases of diarrhea, 8 cases each of pathogen resistance, pyrexia, and vomiting, 7 cases each of acute kidney injury and multiple organ dysfunction syndrome, 6 cases each of renal failure, respiratory failure and seizure, and 5 cases each of encephalopathy and pneumonia.” Overall, no new potential safety concerns have emerged beyond those previously identified.

9.2. Integrated Assessment of Safety

There were 128 pediatric patients exposed to ceftazidime-avibactam in the two studies. There were no deaths and no new safety signals identified. The most common adverse events were diarrhea in the cUTI group and vomiting and infusion site reactions in the cIAI group, which are known cephalosporin class effects. There were no concerning trends in laboratory values or significant ECG findings. There were no cases of anaphylaxis or *C. difficile* associated diarrhea. There are no new concerns based on post-marketing reports. A PubMed search for “pediatric” AND “ceftazidime-avibactam” did not yield any studies with new safety concerns. Overall, the safety profile for cIAI and cUTI in pediatric patients is similar to the adult population.

10 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting convened for this sNDA.

11 Pediatrics

The FDA Pediatric Review Committee (PeRC) was consulted regarding the study designs, timelines, interpretation of study results and labeling recommendations. Additional advice was sought regarding the use of population-PK modeling for dosing recommendations in pediatric patients with renal impairment for which there were insufficient clinical data (for a discussion, please refer to the clinical pharmacology review in section 6).

The trials submitted for this efficacy supplement were pediatric assessments for patients aged ≥ 3 months to 18 years. For younger patients, the ongoing study PMR 2862-3 (D280C00017), will examine the safety and tolerability of AVYCAZ in patients from birth to <3 months (Table 59). This study is being conducted in patients with late-onset sepsis (b) (4)

(b) (4)

(b) (4)

12 Labeling Recommendations

12.1. Prescribing Information

Draft prescribing information was provided within the application, and the following significant labeling changes were made in the course of the review:

Labeling Section	Modifications
INDICATIONS AND USAGE	• Pediatric patients 3 months and older were added to the cIAI (1.1) and cUTI (1.2) indications.
DOSAGE AND ADMINISTRATION	• Added AVYCAZ dosage information for pediatric patients with cUTI and cIAI (2.2). • Added AVYCAZ dosage adjustment information for pediatric patients 2 years of age and older with renal impairment (2.3).
ADVERSE REACTIONS	• Added clinical trial information for pediatric patients (6.1)
USE IN SPECIFIC POPULATIONS	• Added information on pediatric use (8.4) • Added information on pediatric use in patients with renal impairment (8.6)

CLINICAL PHARMACOLOGY	• Added information on pediatric patients (12.3)
CLINICAL STUDIES	• Added clinical trial information to support the use of AVYCAZ in pediatric patients for the treatment of cIAI (14.1) and cUTI (14.2).

12.2. Patient Labeling

Patient labeling was not proposed in this sNDA.

Reviewer Comment: This is acceptable. AVYCAZ is anticipated to be administered to pediatric patients parenterally in a healthcare setting.

13 Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended. At this time, there are no data to indicate the risks associated with AVYCAZ use in the pediatric population are more concerning than in other cephalosporin-class antibacterial drugs. These risks can be communicated in the labeling for AVYCAZ, as is the case for the adult population.

14 Postmarketing Requirements and Commitments

As noted, the studies submitted in this sNDA are pediatric assessments intended to fulfill PMRs associated with the initial approval of AVYCAZ.

15 Appendices

15.1. Financial Disclosure

(b) (6) was an investigator at site (b) (6) for study D4280C00016. He was given $28,123.91 by (b) (6) for consulting on the meningococcal vaccine and for speaking at (b) (6) about the vaccine. Site (b) (6) enrolled (b) (6) to the CAZ-AVI arm and (b) (6) to the cefepime arm. No SAEs occurred at this site.

There were 22 sites between the two studies with investigators who had initially filled out financial disclosure certification forms but for whom updated forms were not obtained. For these cases, the sponsor states, "Please note that a Financial Disclosure Certification (FDC) form for this investigator regarding interest in AstraZeneca has been collected. Post transition from AstraZeneca to Pfizer an updated and signed FDC form regarding interests in AstraZeneca, Pfizer and Allergan could not be collected for this investigator as they are no longer affiliated with the site and attempts to obtain the information were unsuccessful."

Reviewer comment: The compensation that (b) (6) *received is unlikely to affect the study results, as* (b) (6) *patients were enrolled at the clinical site. For the remaining investigators for whom updated financial disclosures could not be obtained, the Applicant appears to have made reasonable, good faith efforts to follow up.*

Covered Clinical Study (Name and/or Number): D4280C00015

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 29		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 9		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): D4280C00016

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 13		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

15.2.1. Individual Study Reviews

D4280C00014: A Phase I Study to Assess the Pharmacokinetics, Safety and Tolerability of a Single Dose of Ceftazidime-Avibactam (CAZ-AVI) in Children From 3 Months of Age to <18 Years Who Are Receiving Systemic Antibiotic Therapy for Suspected or Confirmed Infection

Date(s): July 2013 – October 2014
Sponsor: AstraZeneca, Alderley Park, Cheshire, UK
Clinical Site: 11 sites

METHODS

Study Design: Study 14 was a Phase 1, open-label, single-dose study designed to characterize the pharmacokinetics (PK), safety, and tolerability of a single dose of ceftazidime-avibactam (CAZ-AVI) administered to hospitalized pediatric patients receiving systemic antibiotic therapy for suspected or confirmed infection. The study population and dosing are shown in Table 60. Six samples were collected over 13 hours for patients in Cohorts 1 and 2; 4 samples were collected over 6 hours for patients in Cohorts 3 and 4.

Table 60. Study 14 Population.

Cohort	Age	CAZ-AVI Dose	Number of Patients	Comments
1[a]	≥12 to <18 years	2000 mg ceftazidime and 500 mg avibactam 2-hour IV infusion	At least 8	
2[a]	≥6 to <12 years	Weight <40 kg: 50 mg/kg ceftazidime and 12.5 mg/kg avibactam Weight ≥40 kg: 2000 mg ceftazidime and 500 mg avibactam 2-hour IV infusion	At least 8	
3[a]	≥2 to <6 years	Normal renal function or mild renal insufficiency: 50 mg/kg ceftazidime and 12.5 mg/kg avibactam Moderate renal insufficiency: 25 mg/kg ceftazidime and 6.25 mg/kg avibactam 2-hour IV infusion	At least 8	Dosing for patients in this age group was determined using population PK modeling of the PK data from Cohorts 1 and 2 and safety and tolerability data to select a safe and effective dose based upon anticipated exposure levels.
4	≥3 months to <2 years	Normal renal function or mild renal insufficiency: 50 mg/kg ceftazidime and 12.5 mg/kg avibactam Moderate renal insufficiency: 25 mg/kg ceftazidime and 6.25 mg/kg avibactam 2-hour IV infusion	At least 8 split into 2 groups: ≥3 months to <1 year (at least 4) AND 1 year to <2 years (at least 4)	Dosing for patients in this age group was determined using population PK modeling of the PK data from Cohorts 1 through 3 and safety and tolerability data to select a safe and effective dose based upon anticipated exposure levels. BMI was not calculated for children <2 years of age as BMI is not considered a screening tool for healthy weight in children under 2 years of age.

[a] Patients considered for entry into the study were within the normal range of BMI for their age (2 to <18 years). A healthy BMI for this age group falls between the 5th percentile and ≤95th percentile according to height, weight, and age.
Abbreviations: BMI, body mass index; CAZ-AVI, ceftazidime in combination with avibactam; PK, pharmacokinetic

Analytical Method: Bioanalytical assay HB-13-001 was used to measure the concentrations of ceftazidime and avibactam in plasma. The performance was satisfactory.

RESULTS

A total of 35 patients were enrolled in the study including 11 in Cohort 1, 8 in Cohort 2, 8 in Cohort 3, and 8 in Cohort 4.

Pharmacokinetics:

Table 61 shows the calculated PK parameters.

Table 61. PK of Single Doses of Ceftazidime and Avibactam. Geometric Mean (CV%)[a]

	Cohort 1		Cohort 2		Cohort 3		Cohort 4	
	CAZ	AVI	CAZ	AVI	CAZ	AVI	CAZ	AVI
$AUC_{0-\infty}$ (µg*h/mL)	231 (31)	36.4 (34)	221 (18)	34.8 (23)	N/A	N/A	N/A	N/A
C_{max} (µg)	79.8 (42)	15.1 (52)	81.3 (18)	14.1 (23)	80.1 (15)	13.7 (22)	91.7 (20)	16.3 (23)
$T_{1/2}$ (hr)	1.65 (0.937,2.83)	1.5 (0.887,2.76)	1.63 (0.917,1.79)	1.66 (0.893, 2.02)	N/A	N/A	N/A	N/A

CAZ = ceftazidime, AVI = Avibactam, CV = coefficient of variation; AUC = area under the curve, N/A = Not applicable; $T_{1/2}$ reported as median (minimum, maximum)

Due to sparse sampling, the $AUC_{0-\infty}$, and $T_{1/2}$ were not calculated in Cohorts 3 and 4; in particular, the samples may not have been drawn out long enough to fully capture the elimination phase. The PK parameters appear to be reasonably similar among age cohorts with a trend towards higher values of C_{max} in Cohort 4 relative to the other age cohorts.

The study conduct was adequate to measure most of the relevant PK parameters of CAZ-AVI in pediatric patients. 50-12.5 mg/kg CAZ-AVI appeared to be safe and well-tolerated in the pediatric population.

15.2.2. Population PK Analysis

The Applicant updated their previously submitted population PK (PPK) models of ceftazidime (CAZ) and avibactam (AVI), MS-09, with pediatric PK data. Table 62 shows the studies from which data were obtained to generate the new models, MS-PED-02.

Table 62. Clinical Studies Included in Population PK Models MS-PED-02.

Study ID	Phase	Study Type	AVI with Ceftaroline Fosamil, AVI alone, or CAZ-AVI (n)[a]
Adult PK studies			
NXL104/1001	1	Single-ascending dose PK study for AVI alone or CAZ-AVI in healthy volunteers	56
NXL104/1002	1	Multiple-ascending dose PK study for AVI alone or CAZ-AVI in healthy volunteers	41
NXL104/1003	1	Single-dose PK study for AVI for subjects with normal renal function or renal impairment	31
NXL104/1004	1	Single-dose PK study for AVI for young, elderly, male, or female healthy volunteers	33
D4280C00010	1	Single- and multiple-dose PK study of AVI alone or CAZ-AVI in Japanese healthy volunteers	13
D4280C00011	1	Drug-drug interaction between CAZ and AVI	43
CXL-PK-01	1	Ceftaroline fosamil and AVI interaction study and ceftaroline fosamil and AVI combination study (single or multiple dose)	48
CXL-PK-03	1	PK study of ceftaroline fosamil and AVI in subjects with severe renal impairment	16
CXL-PK-04	1	PK study of ceftaroline fosamil and AVI in patients with sepsis and with augmented renal clearance	12
CXL-PK-06	1	PK study of ceftaroline fosamil and AVI in subjects with obesity	40
D4280C00020	1	Single- and multiple-dose PK study of CAZ-AVI in Chinese healthy volunteers	12
NXL104/2001	2	Safety, tolerability, efficacy, PK study of CAZ-AVI in patient with cUTI	68
NXL104/2002	2	Safety, tolerability, efficacy, PK study of CAZ-AVI in patient with cIAI	101

D4280C00001 and D4280C00005 (RECLAIM)	3	Efficacy, safety, tolerability of CAZ-AVI in patients with cIAI	529
D4280C00006 (REPRISE)	3	Safety, tolerability, efficacy, PK study of CAZ-AVI in patient with cUTI or cIAI due to infection of CAZ-resistant pathogen	162
D4280C00002/ D4280C00004 (RECAPTURE)	3	Efficacy, safety, tolerability of CAZ-AVI in patients with cUTI	498
D4280C00018 (RECLAIM 3)	3	Efficacy, safety, tolerability of CAZ-AVI in Asian patients with cIAI	195
D4281C00001 (REPROVE)	3	Efficacy, safety, tolerability of CAZ-AVI in patients with NP, including HAP and VAP	413
Pediatric PK studies			
D4280C00014	1	Single-dose PK, safety, tolerability study of CAZ-AVI in children from 3 months to < 18 years of age who are receiving systemic antibiotic therapy for suspected or confirmed infection	32
D4280C00015 /C3591004	2	Multiple-dose, safety, tolerability, PK, efficacy study of CAZ-AVI when given in combination with metronidazole, and when compared with meropenem, in children with cIAIs from 3 months to < 18 years of age	61
D4280C00016 /C3591005	2	Multiple-dose, safety, tolerability, PK, efficacy study of CAZ-AVI compared with cefepime in children with cUTIs from 3 months to < 18 years of age	67

Abbreviations: AVI = avibactam; CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; ID = identification; NP = nosocomial pneumonia; PK = pharmacokinetic(s); VAP = ventilator-associated pneumonia.

[a] Number of patients in the dataset for a given study.

The final models for ceftazidime (CAZ) and avibactam (AVI) both used 2-compartment structures. Weight-based allometric scaling was used with an exponent of 1 for central volume (V1) and peripheral volume 2 (V2) and with an exponent of 0.67 for total clearance (CL) and intercompartmental clearance (Q), except for CAZ CL which used a sigmoidal function to describe the relationship between weight and CL. The final PK parameters of CAZ and AVI in the previous models (MS-09, adult data only) and current models (MS-PED-02, adult and pediatric data) are shown in Table 63 and Table 64, respectively.

Table 63. CAZ Parameter Estimates from Population PK Models MS-PED-02 and MS-09.

Parameters	MS-PED-02			MS-09		
Fixed Effects	**Estimate**	**%RSE**	**BSV (CV%)**	**Estimate**	**%RSE**	**BSV (CV%)**
Slope 1: NCrCL < 100 mL/min, Slope 1 × NCrCL	0.01030360 (Fixed)	-	-	0.0103	0.409	-
Slope 2: NCrCL ≥ 100 mL/min, Slope 1* 100 + Slope 2 * (NCrCL - 100)	0.00125182 (Fixed)	-	-	0.00125	8.84	-
CL (L/h)	7.75	1.56	40.8	6.95	1.7	42.3
Vc (L)	11.2	3.54	33.8	10.5	13.1	105
Q (L/h)	5.33	6.52	47.5	31.5	18.8	259
Vp (L)	6.52	3.12	15.4	7.57	9	110
WT at half-maximal effect of WT on CL (kg) Emax function	53.5	8.81	-	-	-	-
Effect of cIAI on CL	1.33	2.37	-	1.16	2.2	-
Effect of NP on CL	1.1	2.96	-	0.999	2.4	-
Race effect on CL (ASN)	-0.136	20.3	-	-0.161	11.8	-
Race effect on CL (CHN)	-0.0844	29.1	-	-0.0855	27	-
Effect of cUTI on Vc	1.49	4.57	-	1.03	11.1	-
Effect of cIAI or NP on Vc	1.83	3.97	-	1.14	9.9	-
Effect of ventilator on Vc	0.202	33.5	-	0.297	45.4	-
Race effect on Vc (ASN, CHN, and JPN)	-0.135	23.2	-	-0.27	18.6	-
WT effect on Vc	-	-	-	1.01	12.6	-
Effect cUTI/acute pyelonephritis on Vc	-	-	-	-0.185	41.2	-
Inter-subject variability	**Estimate**	**%RSE**	**Shrinkage (%)**	**Estimate**	**%RSE**	**Shrinkage (%) or correlation**
ηCL2	0.154	2.62	10.5	0.179	3.3	11.4
ηVc2	0.108	11.76	50.1	1.10	10.2	31.2
ηVc-ηCL covariance	-	-	-	-0.189	15.2	r=-0.42
ηQ2	0.203	18.98	79.7	6.70	15.5	27.46
ηQ-ηCL covariance	-	-	-	0.883	10.1	r=0.81
ηQ-ηVc covariance	-	-	-	-0.643	43.1	r=-0.24
ηVp2	0.0236	21.12	83.2	1.21	8.8	17.5
ηVp-ηCL covariance	-	-	-	0.383	5.1	r=0.82
ηVp-ηVc covariance	-	-	-	-0.972	7.3	r=-0.84
ηVp-ηQ covariance	-	-	-	1.73	14.5	r=0.61
Residual error	**-**	**-**	**-**			
Proportional variability, Phase 1	0.172	10.4	-	0.04	0.5	-
Additive variability, Phase 1 (ng/mL)	125	15.9	-	26489	7.5	-
Proportional variability, Phase 2 or 3	0.374	2.21	-	0.114	2.1	-
Additive variability, Phase 2 or 3 (ng/mL)	2560	23.1	-	18.4	447	-

Table 64. AVI Parameter Estimates from Population PK Models MS-PED-02 and MS-09.

	MS-PED-02			MS-09		
Parameter	**Estimate**	**%RSE**	**BSV (CV%)**	**Estimate**	**%RSE**	**BSV (CV%)**
CL (L/h)	10.7	3.74	58.8	10.2	1.8	59.1
Vc (L)	11.5	4.31	107	11.1	9.9	107.1
Vp (L)	7.56	14.1	108	6.91	6.5	252.2
Q (L/h)	6.94	18.5	234	5.44	13.9	122.2
Effect of ESRD on CL	0.0674	23.7	-	0.0678	8.3	-
CL estimate for dialysis patients (L/h)	21.1	9.5	-	20.8	9.6	-
Power NCrCL (< 80 mL/min/1.73 m2) on CL	0.986	6.34	-	1.05	2.4	-
Linear NCrCL (≥ 80 mL/min/1.73 m2) on CL	0.00344	11.6	-	0.00279	3.7	-
Effect of cIAI on Vc (Phase 2)	2.17	24.8	-	1.92	25.4	-
Effect of cIAI on CL (adult, Phase 2)	0.431	33.4	-	0.406	23.2	-
Effect of cUTI on Vc	0.412	19.6	-	0.434	24	-
Effect of cIAI (Phase 3), NP, pediatric cIAI on Vc	0.214	26.8	-	0.329	28.6	-
Effect of APACHE II on CL	-0.192	15.4	-	-0.197	8.7	-
Effect of ventilator (POP5) on Vc	0.267	55.6	-	0.175	53.3	-
Scaling factor for CrCL in subjects with augmented renal clearance	-	-	-	0.992	17.4	-
WT on Vc	-	-	-	1.08	7.8	-
Effect of Race on CL (non-Chinese, non-Japanese Asian)	-	-	-	-0.0865	20.2	-
Inter-subject variability	**Estimate**	**%RSE**	**Shrinkage (%) or correlation**	**Estimate**	**%RSE**	**Shrinkage (%) or correlational**
ηCL2	0.3453	6.743	6.8	0.349	2	7.29
ηVc-ηCL	0.1305	169.8	r = 0.21a	0.125	15.6	r=0.2
ηVc2	1.139	25.91	32.4	1.147	6	28.15
ηVp-ηCL	0.5397	13.8	r = 0.85a	0.611	3.6	r=0.85
ηVp-ηVc	-0.3397	40.12	r = -0.29a	-0.426	18	r=-0.33
ηVp2	1.156	17.21	12.3	1.494	7	13.52
ηQ-ηCL	1.178	13.78	r = 0.86a	1.231	4.1	r=0.83
ηQ-ηVc	-0.7016	103.8	r = -0.28a	-0.978	16.8	r=-0.36
ηQ-ηVp	2.495	35.26	r = 0.99a	3.059	7.1	r=0.99
ηQ2	5.487	47.83	12.6	6.359	8.1	14.18
Residual error						
Proportional variability, Phase 1	0.174	8.09	-	0.173	0.1	-
Additive variability, Phase 1 (ng/mL)	43.8	23.9	-	44.6	0.5	-
Proportional variability, Phase 2	0.498	4.83	-	0.492	3	-
Proportional variability, Phase 3	0.364	2.6	-	0.363	1.1	-

The MS-PED-02 models for CAZ and AVI do not appear to be significantly different from the previous versions of the models in MS-09. Because the adult model has been previously reviewed, this reviewer will focus the review on the pediatric components.

Description of Age-Related Changes on Clearance

The major addition to the adult structural model (MS-09) to make the current pediatric model (MS-PED-02) is the specification of clearance. Normalized creatinine clearance was defined using the bedside Schwartz equation in children 2-17 yr of age and the BSA-normalized Cockcroft-Gault equation in adults. The creatinine clearance estimate from the Cockcroft-Gault equation was normalized by BSA in order to produce the same units in adults as in children. Bodyweight was then used as a covariate on clearance to incorporate the size of the patient into the definition of clearance. In children under 2 yr of age, a maturation function was used and fixed to values generated from an analysis by Rhodin et al.[3]

The Rhodin paper estimated a maturation function for glomerular filtration rate (GFR) using a PPK approach, with data from 923 patients with ages ranging from a PMA of 22 weeks (premature neonate) to 31 years from 8 studies in which a direct measurement of GFR was performed including methods using polyfructose, ^{51}Cr-EDTA, mannitol, or iohexol. The final Rhodin maturation function used a sigmoidal structure with half-maximal GFR at a PMA of 47.7 weeks and a Hill coefficient of 3.4.

The Applicant attempted to estimate the values of the maturation function using the same structure as the Rhodin analysis. However, the attempt to estimate the values of the maturation function resulted in minimization termination for the CAZ model and an increase in the objective function value for the AVI model with a generally worse model fit.

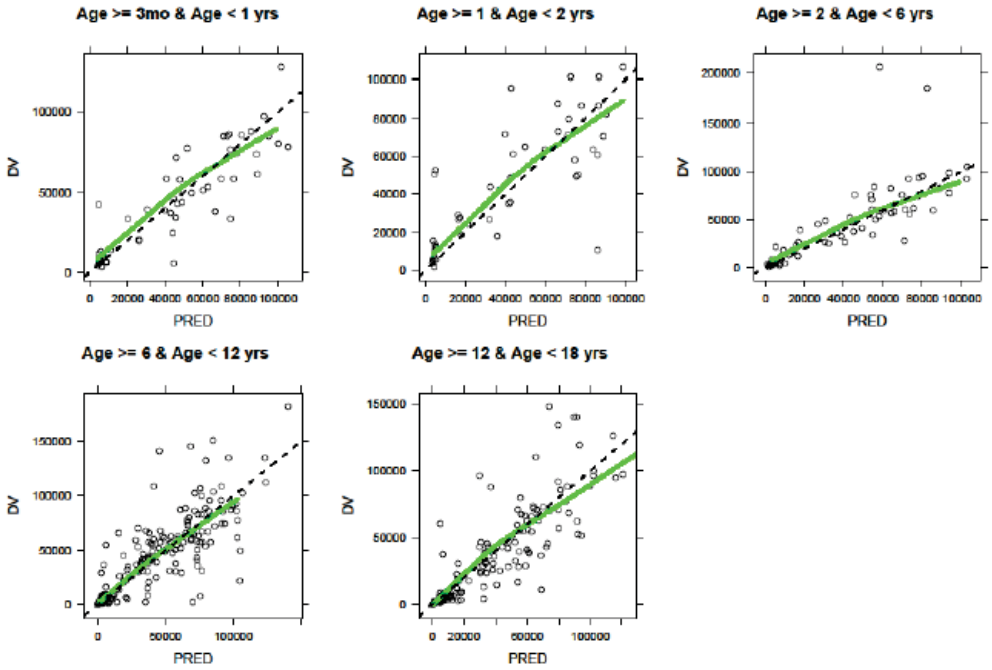
It is possible that the Applicant was unable to properly estimate the maturation function on GFR due to a limited number of pediatric patients less than 2 yr (26), with no patients under 3 months when the most maturation is occurring. The Rhodin analysis agrees with general wisdom on renal maturation and comes from a leader in the field, the Holford group. Considering all the available data, fixing the maturation function to estimates from the Rhodin equation appears to be acceptable.

Goodness of Fit

Dependent variable (DV, representing the concentration) vs population prediction (PRED) plots for CAZ and AVI with a focus on the pediatric age range are shown in Figure 9 and Figure 10, respectively.

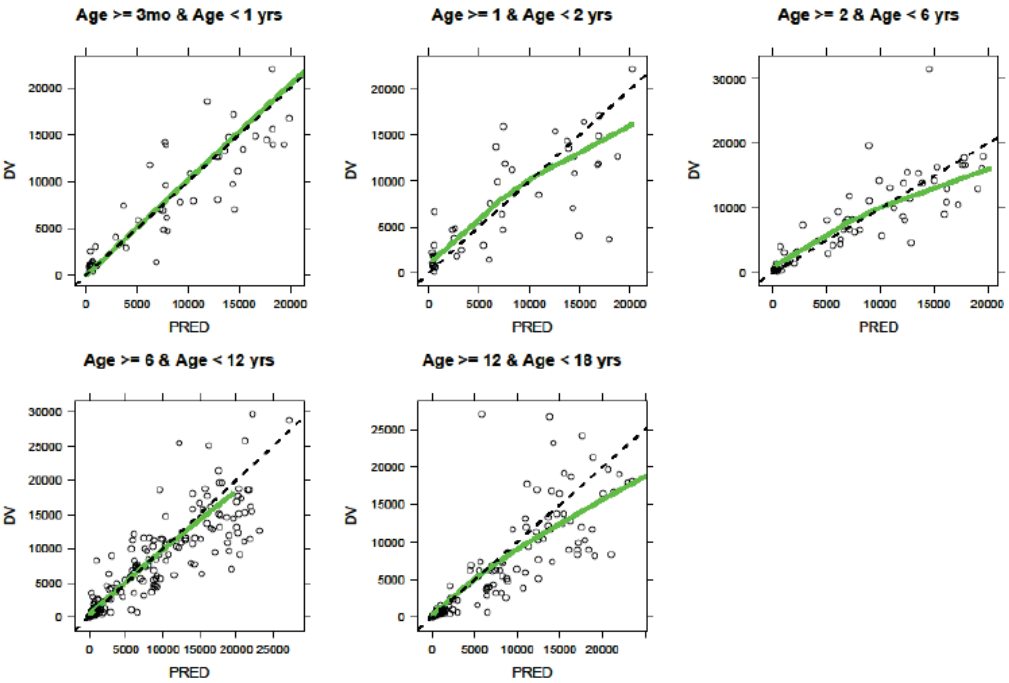
[3] Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76.

Figure 9. CAZ DV vs PRED Stratified by Age Cohorts.



The green line represents the trend of the data relative to the line of unity (dashed line).

Figure 10. AVI DV vs PRED Stratified by Age Cohorts.

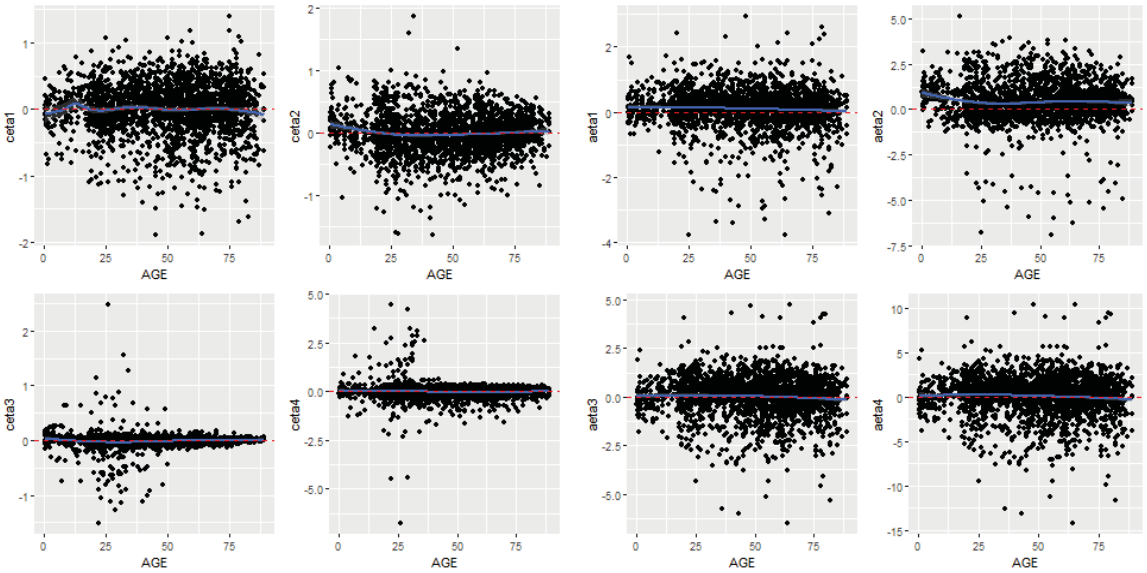


The green line represents the trend of the data relative to the line of unity (dashed line).

Overall, the DV vs PRED plots show reasonably good agreement, with a slight trend towards over-estimation of DV for CAZ and AVI at the higher end of the range (>10,000 ng/mL). Given that the PK/PD targets evaluated in this review for CAZ and AVI are time above MIC and concentration threshold (8000 and 1000 ng/mL, respectively) and the over-estimation occurs well above that, this tendency towards over-estimation likely would not affect the results of the probability of target attainment analysis (PTA).

Figure 11 shows trends in inter-individual variability for CAZ and AVI over the age range of patients included in the CAZ and AVI PPK datasets.

Figure 11. Trends in Inter-Individual Variability (ETA) of Major PK Parameters for CAZ (Left Two Panels) and AVI (Right Two Panels) by Age.



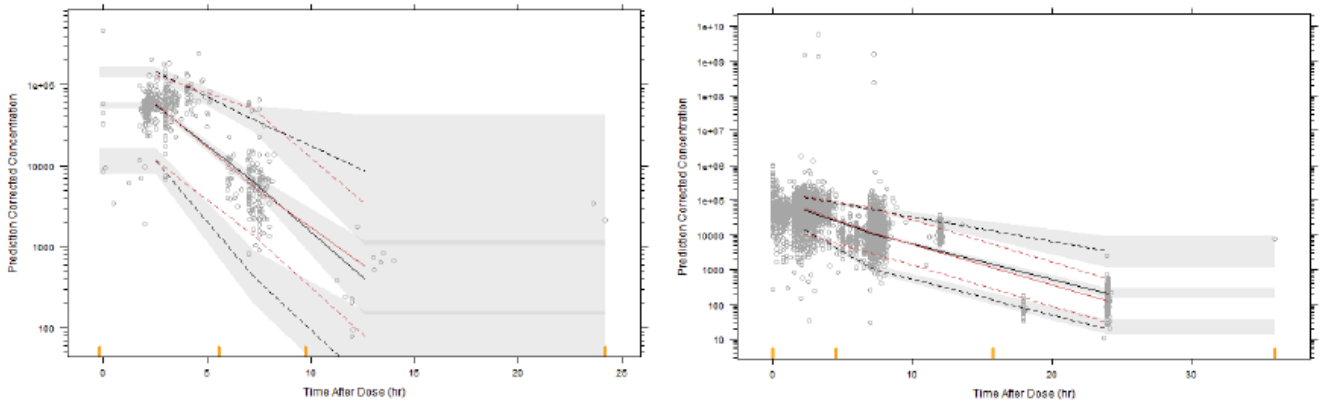
The red dashed lines represent 0, and the blue lines represent the trend of ETA over age.
ceta1-4: ETA for CAZ CL, Vc, Q, and Vp, respectively.
aeta1-4: ETA for AVI CL, Vc, Vp and Q, respectively.

The spread of values of ETA for major PK parameters of CAZ and AVI appear to generally be homoscedastic and balanced throughout the age range, with the exception of Vc where this a slight trend towards higher Vc ETA in children relative to adults. Overall, this trend does not appear to be significant, which indicates that the model was able to describe and link CAZ and AVI PK in adults and children well.

Visual Predictive Checks

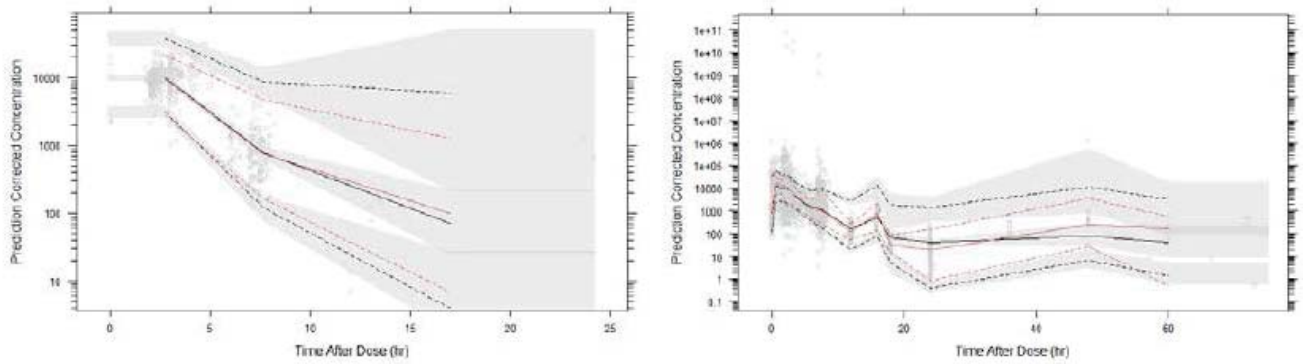
Prediction-corrected visual predictive checks (pcVPC) are shown in Figure 12 and Figure 13 for CAZ and AVI, respectively.

Figure 12. pcVPC for the Final CAZ PK Model in Pediatric Patients (Left) and Adult Patients (Right).



The solid red line represents the median observed concentration. The solid black line represents the simulated median concentration. The shaded are represents the 90% prediction interval of the median and 5th and 95th percentiles. The red and black dashed lines represent the 5th and 90th percentiles of the observed and simulated data, respectively.

Figure 13. pcVPC for the Final AVI PK Model in Pediatric Patients (Left) and Adult Patients (Right). Adapted from CAZ-MS-PED-02 Report Figure 19



Each dot represents a prediction-corrected PK observation. The solid red line represents the median observed concentration. The solid black line represents the simulated median concentration. The shaded are represents the 90% prediction interval of the median and 5th and 95th percentiles. The red and black dashed lines represent the 5th and 90th percentiles of the observed and simulated data, respectively.

The pcVPC plots for the final CAZ and AVI models show reasonable agreement between the observed and predicted values. The 5th percentile of the observed CAZ concentrations appears to be underestimated by the model; however, this would not lower efficacy and is unlikely to affect safety. The 90th percentile of the observed AVI concentrations appears to be overestimated; however, this would likely not affect efficacy because both the observed and simulated data are well above the PK-PD target for AVI, 1000 ng/mL. The variability appears to be higher in the pediatric patients; however, this is likely due to the larger axis scale in the pcVPC for adult patients.

Overall, the PPK models for CAZ and AVI in MS-PED-02 appear to describe the PK data reasonably well and are acceptable to be used for simulation and PTA analysis.

15.2.3. Target Attainment Analysis

Applicant's Analysis of Target Attainment at the Applicant-Proposed Dose

In order to support efficacy in pediatric patients, the Applicant conducted a probability of PK-PD target attainment (PTA) analysis. The PK-PD targets for CAZ and AVI are 50% free time above MIC and 50% free time above 1 mg/L, respectively. Because the *in vitro* test susceptibility criteria (breakpoint) is 8 mg/L in adults, 8 mg/L was chosen as the target MIC for the current PTA analysis.

Using the final PK datasets, the Applicant resampled values of weight, age, and inter-individual variability (IIV, ETA) stratified by the following age cohorts to create pseudopopulations of 1000 patients each: 3-6 months, 6-12 months, 1-2 years, 2-6 years, 6-12 years, 12-18 yr, and adults. The CDC growth charts were also used to provide supplemental values of age and weight. Each pseudopopulation was simulated at varying levels of renal function: normal (80-150 mL/min/1.73m^2), mild renal impairment (50-80 mL/min/1.73m^2), and moderate renal impairment (30-50 mL/min/1.73m^2). To avoid bias, the Applicant re-inflated the values of IIV by the shrinkage. The Applicant then simulated the PK profiles of each patient without residual error. The simulated PK profiles were used to calculate the percentage of each population reaching the joint targets of CAZ and AVI. The results of the Applicant's PTA analysis at the Applicant-proposed dose are shown in the Table 65, Table 66, and Table 67.

Table 65. Percentage of Patients with Normal Renal Function Achieving the Joint PK/PD Target Following Repeated Administration of CAZ-AVI at the Proposed Dose at an MIC of 8 Mg/L.

Age Group	Dose [a] (CAZ/AVI)	Joint PTA at an MIC of 8 mg/L (%) [b]		
		cIAI	cUTI	HABP/VABP
12 to < 18 years	50/12.5 mg/kg q8h	96	99	99
6 to < 12 years	50/12.5 mg/kg q8h	90	97	97
2 to < 6 years	50/12.5 mg/kg q8h	82	94	92
1 to < 2 years	50/12.5 mg/kg q8h	82	94	92
6 to < 12 months	50/12.5 mg/kg q8h	90	98	97
3 to < 6 months	40/10 mg/kg q8h	93	98	98
Adults	2000/500 mg q8h	95	97	95

[a] All doses as a 2-hour IV infusion with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > C_T of 1 mg/L for avibactam.

Table 66. Percentage of Patients with Mild Renal Impairment Achieving the Joint PK/PD Target Following Repeated Administration of CAZ-AVI at the Proposed Dose at an MIC of 8 Mg/L.

Age Group	Dose [a] (CAZ/AVI)	Joint PTA at an MIC of 8 mg/L (%) [b]		
		cIAI	cUTI	HABP/VABP
12 to < 18 years	50/12.5 mg/kg q8h	99	99	99
6 to < 12 years	50/12.5 mg/kg q8h	100	100	100
2 to < 6 years	50/12.5 mg/kg q8h	100	100	100
Adults	2000/500 mg q8h	99	99	99

[a] All doses as a 2-hour IV infusion with a maximum dose of 2000 mg ceftazidime and 500 mg avibactam.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > C_T of 1 mg/L for avibactam.

Table 67. Percentage of Patients with Moderate Renal Impairment Achieving the Joint PK/PD Target Following Repeated Administration of CAZ-AVI at the Proposed Dose at an MIC of 8 Mg/L.

Age Group	Dose [a] (CAZ/AVI)	Joint PTA at an MIC of 8 mg/L (%) [b]		
		cIAI	cUTI	HABP/VABP
12 to < 18 years	25/6.25 mg/kg q8h	99	99	99
6 to < 12 years	25/6.25 mg/kg q8h	100	100	100
2 to < 6 years	25/6.25 mg/kg q8h	100	100	100
Adults	1000/250 mg q8h	99	99	99

[a] All doses as a 2-hour IV infusion with a maximum dose of 1000 mg ceftazidime and 250 mg avibactam.
[b] PK/PD target of 50% fT > MIC of 8 mg/L for ceftazidime and 50% fT > C_T of 1 mg/L for avibactam.

Reviewer Analysis of Target Attainment at the Proposed Dose

Due to potential bias in the generation of the populations in the Applicant's approach (resampling IIV stratified by age, no use of residual error), this reviewer used the final models of CAZ and AVI to perform an additional PTA analysis. The reviewer's analysis resampled IIV from the entire population irrespective of age, used residual error, and assumed that there was no relationship between CAZ parameters and AVI parameters although it is likely that the PK parameters of CAZ and AVI are correlated because they are both >80% renally cleared. The combination of these factors results in a PK profile that is more variable. The reviewer's simulation and PTA analysis using a more variable PK profile were designed to produce a more conservative estimate of PTA, outlining a worse potential scenario. Because of this more conservative approach to the PTA analysis, lower values of PTA are acceptable, i.e. > 80% target attainment.

For the PTA analysis, a pseudopopulation of over 3000 patients was created for the reviewer's analysis based on the CDC growth charts. Stratified by age in weeks, values of weight were

sampled assuming a normal distribution. Values of inter-individual variability and residual error were selected based on the variance-covariance matrix identified in the final models. Normalized creatinine clearance was selected using a random uniform distribution from 0 to 150 ml/min/1.73m^2. 100 repetitions of the simulation were performed. Because exposure is higher in patients with cUTI relative to patients with cIAI, patients with cIAI had lower target attainment than patients with cUTI; thus, cIAI was the focus of the reviewer's PTA analysis. Additionally, PTA was calculated on Day 2. Because of the short half-lives of CAZ and AVI (<3 hr), most patients with normal renal function will reach steady-state by Day 2, and the exposures and values of PTA would not be significantly lower on Day 1.

Table 68 shows the PTA in patients administered CAZ-AVI at the proposed dose on Day 2.

Table 68. Percentage of Patients Achieving the CAZ-AVI PK/PD Joint Target Following Administration of CAZ-AVI at the Proposed Dose on Day 2 at an MIC of 8 Mg/L.

Normalized Creatinine Clearance (mL/min/1.73m^2)		0-5	6-15	16-30	31-50	51-80	81-150	81-150
Infusion Duration (hr)		2						3
Age (yr)	0.25-0.5	-	-	-	-	-	89%	95%
	0.5-1	-	-	-	-	-	84%	94%
	1-2	-	-	-	-	-	78%	92%
	2-6	94%	94%	95%	97%	95%	77%	90%
	6-12	96%	96%	97%	98%	97%	86%	95%
	12-18	96%	96%	97%	98%	98%	91%	97%
	18-20	92%	92%	96%	98%	98%	89%	96%

The PTA analysis conducted by the reviewer generally agrees with the PTA analysis conducted by the Applicant, with a slight trend towards lower PTA likely due to the more conservative assumptions in the reviewer's approach. Only patients between 1-6 yr with normal renal function have a PTA below 80%, but administering CAZ-AVI with an infusion duration of 3 hr increases the target attainment above 90%.

Overall, the PTA analysis conducted by the Applicant and the reviewer demonstrate that the proposed dose appears to be adequate in patients across a wide range of age and creatinine clearance. The PTA analysis also validates the Applicant's claim that administering CAZ-AVI a 3-hr infusion will ensure high target attainment.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EVA ZUFFOVA
03/13/2019 12:06:45 PM

SUMATHI NAMBIAR
03/13/2019 12:54:22 PM
Concur with the review team's assessment and recommendations.