NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	206494/S-012
Priority or Standard	Priority
Submit Date(s)	7/28/2023
Received Date(s)	7/28/2023
PDUFA Goal Date	1/28/2024
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	See electronic signature date
Established/Proper Name	Ceftazidime-avibactam
Trade Name	AVYCAZ
Pharmacologic Class	Cephalosporin (beta-lactam) and beta-lactamase inhibitor combination antibacterial drug
Code name	N/A
Applicant	AbbVie, Inc.
Dosage form	Injection, supplied as a sterile powder for constitution in single dose vials
Applicant proposed Dosing Regimen	Dosing based on age, weight, and renal function; see review for details
Applicant Proposed Indication(s)/Population(s)	Treatment of pediatric patients birth to < 3 months of age with the following infections caused by designated susceptible gram-negative microorganisms: • Complicated intra-abdominal infections (cIAI) • Complicated urinary tract infections (cUTI) • Hospital-acquired bacterial pneumonia (HABP) and Ventilator-associated bacterial pneumonia (VABP)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Nosocomial pneumonia (SCTID: 425464007) Infectious disease of abdomen (SCTID: 128070006) Urinary tract infectious disease (SCTID: 68566005)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of pediatric patients from birth (gestational age at least 31 weeks) to < 3 months of age with the following infections caused by designated susceptible gram-negative microorganisms: • Hospital-acquired bacterial pneumonia (HABP) and Ventilator-associated bacterial pneumonia (VABP) • Complicated intra-abdominal infections (cIAI), used in combination with metronidazole • Complicated urinary tract infections (cUTI) including pyelonephritis
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Nosocomial pneumonia (SCTID: 425464007) Ventilator-acquired pneumonia (SCTID: 429271009) Infectious disease of abdomen (SCTID: 128070006) Urinary tract infectious disease (SCTID: 68566005)
Recommended Dosing Regimen	Dosing based on age and weight; see review for details

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Abbreviations: DEPI=Division of Epidemiology, DMEPA=Division of Medication Error Prevention and Analysis, DPMH=Division of Pediatric and Maternal Health, DPV=Division of Pharmacovigilance, OPDP=Office of Prescription Drug Promotion, OPQ=Office of Pharmaceutical Quality, OSE=Office of Surveillance and Epidemiology, OSIS=Office of Study Integrity and Surveillance

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Glossary

AE	adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	area under the curve
AVI	Avibactam
CAZ	Ceftazidime
CDAD	*Clostridoides difficile* associated diarrhea
CFR	Code of Federal Regulations
CRF	case report form
cIAI	complicated intra-abdominal infection
CNS	Central nervous system
CRE	carbapenem-resistant Enterobacterales
CSR	clinical study report
cUTI	complicated urinary tract infection
DPMH	Division of Pediatric and Maternal Health
DPV	Division of Pharmacovigilance
DTR	Difficult-to-Treat Resistance
ECG	electrocardiogram
EMA	European Medicines Agency
EOIV	End of IV Treatment
EOT	End of treatment
ESBL	Extended-spectrum beta-lactamase
FDA	Food and Drug Administration
FAERS	Food and Drug Administration Adverse Event Reporting System
g	grams
GA	gestational age
GCP	good clinical practice
HABP	hospital-acquired bacterial pneumonia
IND	Investigational New Drug
ITT	intent to treat
IV	intravenous
kg	kilograms
KPC	*Klebsiella* pneumoniae carbapenemase
LFU	Late Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mg	milligrams
MDR	multi-drug resistant
MIC	Minimum inhibitory concentration
NEC	necrotizing enterocolitis
NDA	new drug application

NP	Nosocomial pneumonia
OAT	Organic anion transports
OCS	Office of Computational Science
OPAT	Outpatient parenteral antimicrobial therapy
OPQ	Office of Pharmaceutical Quality
OprD	Outer membrane porin D
OSIS	Office of Study Integrity and Surveillance
OXA	Oxacillinases
PAH	p-aminohippuric acid
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	prescribing information
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PT	Preferred Term
PTA	Probability of target attainment
PsA	*Pseduomonas aeruginosa*
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SOC	System Organ Class
TOC	Test of cure
TEAE	treatment emergent adverse event
UTI	urinary tract infection
VABP	ventilator-associated bacterial pneumonia

1. Executive Summary

1.1. Product Introduction

AVYCAZ (CAZ-AVI) is a fixed combination antibacterial drug composed of ceftazidime, a third-generation cephalosporin, and avibactam, a non-β-lactam β-lactamase inhibitor that does not have antibacterial activity at the labeled dose but protects ceftazidime from degradation by a range of bacterial beta-lactamases (Ambler Class A, Class C, and some Class D enzymes). Ceftazidime was first approved in 1985 (FORTAZ, NDA 050578) 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.

AVYCAZ was initially approved in February 2015 for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in adult patients with limited or no alternative treatment options. Two subsequent efficacy supplements (S-002 for cIAI and S-003 for cUTI) provided clinical trial data in adult patients to support the removal of the limited use statements. An additional efficacy supplement (S-004) provided clinical trial data to support an indication for treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adult patients. The dosing of AVYCAZ is the same across indications for patients aged 18 years and older, 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.

Pediatric efficacy supplements were subsequently approved based on data from pediatric clinical studies of AVYCAZ supporting extension of the approved indications for treatment of cUTI (S-005), cIAI (S-006), and HABP-VABP (S-011) in pediatric patients ≥3 months to <18 years of age. The approved AVYCAZ pediatric dosing is age- and weight-based for all indications: 62.5 mg/kg (up to a maximum of 2.5 g) in patients 2 years to < 18 years of age, 62.5 mg/kg in patients 6 months to < 2 years of age, and 50 mg/kg in patients 3 months to < 6 months of age. Dosing is modified for patients with renal impairment who are at least 2 years of age; there is insufficient information to recommend a dosing regimen in patients < 2 years of age with renal impairment.

This efficacy supplement (S-012) proposes to extend the approved indications for treatment of cUTI, cIAI, and HABP/VABP to pediatric patients from birth to < 3 months of age. The supplement was submitted in response to Pediatric Research Equity Act (PREA) post marketing requirement (PMR) 2862-3 for AVYCAZ. The submission contains data from an open-label single-and multiple-dose PK and safety study of AVYCAZ enrolling neonates (full-term and pre-term) and infants < 3 months of age with suspected or confirmed infections due to gram-negative pathogens requiring IV antibacterial treatment. The study evaluated the following age- and weight-based AVYCAZ dosing: 37.5 mg/kg in infants > 28 days but < 3 months of age and 25 mg/kg in neonates from birth to 28 days of age.

The Applicant was granted two pediatric deferral extensions for PMR 2862-3, with the final study report due date extended from December 2020 to September 2023. The study initially planned to enroll 48 pediatric patients with evaluable PK data equally divided into 3 age cohorts but encountered difficultly completing enrollment of the multiple-dose cohort evaluating full-term neonates from birth to 28 days of age, ultimately enrolling 4 of 8 planned PK-evaluable patients in this cohort. The submission includes population PK models to support proposed dosing from birth (gestational age 31 weeks and older) to 3 months of age.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness to support the approval of AVYCAZ for treatment of cUTI, cIAI, and HABP/VABP caused by susceptible gram-negative microorganisms in pediatric patients from birth (gestational age at least 31 weeks) to < 3 months of age was extrapolated from adequate and well-controlled trials of AVYCAZ treatment for cUTI, cIAI, and HABP/VABP in adults. Extrapolation is supported by the similarities in the pathophysiology of these infections and the responsible pathogens in adult and pediatric populations as well as the exposure comparisons between pediatric and adult patients at the proposed AVYCAZ doses (see Section 6.2). The extrapolation is further supported by the joint ceftazidime-avibactam probability of target attainment findings in pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ceftazidime-avibactam (AVYCAZ; AVYCAZ®) is a fixed-dose combination of ceftazidime, a third-generation cephalosporin, and avibactam, a non-β-lactam β-lactamase inhibitor which restores ceftazidime's activity against beta-lactamase producing gram-negative bacteria. AVYCAZ is approved for the treatment of complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI) including pyelonephritis, and hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible gram-negative microorganisms in the pediatric and adult population aged 3 months and older. This efficacy supplement proposes to extend the cIAI, cUTI, and HABP/VABP indications from birth to 3 months of age. The dosing regimen for all pediatric indications is age- and weight-based, administered every 8 hours by intravenous (IV) infusion over 2 hours for 5 to 14 days (cIAI) or 7 to 14 days (cUTI including pyelonephritis or HABP/VABP).

Study C3591024 was designed with a planned enrollment of 48 neonates and infants. This was a 2-part, phase 2a, non-randomized, multicenter, open-label, single and multi-dose pharmacokinetic (PK) study to assess PK, safety, and tolerability of AVYCAZ in neonates and young infants from birth (gestational age ≥ 31 weeks) to < 3 months of age (89 days) with suspected or confirmed infections due to gram-negative pathogens requiring IV antibacterial treatment. Forty-six subjects received AVYCAZ: 25 subjects in the single-dose Part A and 21 subjects in the multiple dose Part B. The safety profile of AVYCAZ in Study C3591024 was similar to that in pediatric patients ≥ 3 months of age and in adult patients with cIAI, cUTI, or HABP/VABP treated with AVYCAZ. There have been no new safety signals identified in post-marketing reports since approval of the most recent pediatric efficacy supplement.

Based on similarities in PK, cIAI, cUTI, and HABP/VABP pathophysiology, and the microbiology of these infections in adults and pediatric patients, the efficacy of AVYCAZ for these indications can be extrapolated to the infant and neonate population from trials in the adult population. AVYCAZ has demonstrated *in vitro* activity against Enterobacterales in the presence of some beta-lactamases and extended-spectrum beta-lactamases (ESBLs) of the following groups: TEM, SHV, CTX-M, *Klebsiella* pneumoniae carbapenemase (KPCs), AmpC, and certain oxacillinases (OXA). AVYCAZ also has demonstrated *in vitro* activity against *P. aeruginosa* in the presence of some AmpC beta-lactamases, and certain strains lacking outer membrane porin D (OprD). AVYCAZ is not active against bacteria that produce metallo-beta lactamases and may not have activity against gram-negative bacteria that overexpress efflux pumps or have porin mutations.

AVYCAZ has a favorable safety and efficacy profile for the treatment of cIAI, cUTI, or HABP/VABP caused by susceptible gram-negative microorganisms. Neonates and infants < 3 months of age with cIAI, cUTI, or HABP/VABP are a patient population often with comorbid medical conditions and a significant risk for disease progression and death without effective antibacterial therapy. There are limited treatment options for infants and neonates with cIAI, cUTI, or HABP/VABP caused by multi-drug resistant (MDR) gram-negative pathogens. Salvage therapies often have significant toxicities. The approval of AVYCAZ for treatment of cIAI, cUTI, or HABP/VABP in neonates and infants from birth

(gestational age ≥ 31 weeks) to 3 months of age would help fulfill an unmet need. The risks associated with the use of AVYCAZ in the infant and neonate population can be adequately addressed through the product labeling and routine postmarketing surveillance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• cIAI is defined as an abdominal infection extending beyond the hollow viscus of origin into the peritoneal space. The major pathogens in cIAI are coliforms and other gram-negatives including anaerobes. In the first month of life, the most common causes of cIAI are necrotizing enterocolitis (NEC) or spontaneous intestinal perforation. In older children and adults, the most common cIAI is due to ruptured appendicitis. • All UTIs in neonates and infants are considered complicated due to being associated with anatomic abnormalities and the risk of long-term renal insufficiency. Symptoms of UTI in infants are nonspecific including fever, poor feeding, vomiting, diarrhea, or lethargy. The incidence of UTI is highest among uncircumcised boys or those with anatomical abnormalities, most often vesicoureteral reflux. The most common bacterial etiology for neonatal UTI is *E.coli*, however, other gram-negative pathogens are more common in neonates compared with other age groups including *Klebsiella pneumoniae*, *Proteus* species, and *Enterobacter* species. • HABP has an incidence of 12% in hospitalized children and VABP occurs in 4.3 cases per 1,000 ventilator-days in children under 120 days old. Gram-negative pathogens are frequently the cause of HABP/VABP.	• cIAI, cUTI, and HABP/VABP are serious bacterial infections that are commonly caused by gram-negative pathogens. Pathogens with resistance to multiple classes of existing antibacterial drugs are associated with an increased risk of treatment failure and death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are limited treatment options for cIAI, cUTI, or HABP/VABP that are caused by antibacterial drug resistant gram-negative pathogens, such as ESBL-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), or *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR) in neonates and infants < 3 months. • AVYCAZ requires the addition of metronidazole for anaerobic coverage in the treatment of cIAI.	• There are limited treatment options for cIAI, cUTI, or HABP/VABP due to MDR pathogens. Salvage therapies often have significant toxicities. • AVYCAZ offers an important treatment option for neonates and infants < 3 months of age with cIAI, cUTI, or HABP/VABP.
Benefit	• The efficacy of AVYCAZ for the treatment of cIAI, cUTI, or HABP/VABP has been established in adults. • The primary objective of Study C3591024 was to establish the PK, safety, and tolerability of AVYCAZ in neonates and infants < 3 months of age. Efficacy was a secondary endpoint, and the study was not powered for statistical inference testing. • In Study C3591024, drug exposures in pediatric subjects from birth (gestational age ≥ 31 weeks) to < 3 months of age were reasonably comparable to adults at the proposed doses for ceftazidime and avibactam.	• Based on similarities in PK, disease pathophysiology, and microbiology in both adults and pediatric subjects, Study C3591024 supports the extrapolation of efficacy of AVYCAZ from adults to neonates (gestational age ≥ 31 weeks) and infants < 3 months of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Risks are described in the current AVYCAZ labeling based upon safety data from adult and pediatric populations > 3 months of age with cIAI, cUTI, or HABP/VABP treated with AVYCAZ. The currently labeled adverse reactions are similar to other cephalosporin antibacterials. • Key safety concerns for AVYCAZ include *C.difficile*-associated diarrhea (CDAD), hypersensitivity reactions, and seizure, all of which appear as warnings in the product labeling. These adverse reactions were not observed in Study C3591024. • TEAEs and SAEs occurred at a similar rate in Study C3591024 as in the AVYCAZ safety database from prior adult and pediatric studies. • No new safety signals in the neonate and infant population < 3 months of age were identified in Study C3591024. Therefore, no new warnings are recommended. • There are no new safety signals in post-marketing reports.	• The safety profile in neonates and infants < 3 months was comparable to the previously established safety profile in the pediatric population ≥ 3 months and adult populations with cIAI, cUTI, or HABP/VABP treated with AVYCAZ. • The most serious potential adverse reactions described in the AVYCAZ prescribing information (e.g., CDAD, hypersensitivity reactions, seizure) were not observed in the neonate and infant population most likely due to the small size of the study population. • Routine postmarketing surveillance activities are recommended. There are no safety signals or potential for safety issues that require a Risk Evaluation and Mitigation Strategy (REMS).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
□	**The patient experience data that were submitted as part of the application include:**			
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
x	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Complicated intra-abdominal infections (cIAI); complicated urinary tract infections (cUTI); hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in children 0 to 3 months of age are often caused by gram-negative microorganisms. Antibacterial resistance rates in the United States are increasing. The incidence of carbapenem-resistant Enterobacterales (CRE) increased by 1.5% (from 0.4 to 1.9%) from 1997-2000 to 2013-2016 time periods in the United States (Castanheira, et al., 2019). Risk factors for CRE include receipt of antipseudomonal antibacterial therapy within the previous 3 months; prior surgery; or mechanical ventilation (Chiotos, et al., 2017). CRE infections are associated with a higher 30-day mortality compared with carbapenem-susceptible Enterobacterales (Chiotos, et al., 2018). In addition to CRE, increased incidence of antibacterial resistance in Enterobacterales was also seen with the multi-drug resistant (MDR) phenotype increasing by 7.0% (from 2.7% to 9.7%); and ESBL phenotype increasing by 10.9% (from 4.8% to 15.7%) from 1997-2000 to 2013-2016 time periods in the United States (Castanheira, et al., 2019). The prevalence of antibacterial resistance is highest among *Pseudomonas aeruginosa* (PsA) with about 25% of isolates being MDR. Pan drug resistant PsA isolates are rare, 0.1% of isolates, but have been detected from intra-abdominal infections (0.5%), bloodstream infections (0.1%), and pneumonia in hospitalized patients (0.1%) (Shortridge, et al., 2019).

A cIAI is defined as an abdominal infection that "extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis" (Solomkin, et al., 2010)). The major pathogens in community-acquired intra-abdominal infections are coliforms (Enterobacterales, especially *Escherichia coli)* and anaerobes. Healthcare-associated intra-abdominal infections are commonly caused by more resistant flora including ESBL *Klebsiella* and *E.coli*, *Enterobacter* species, *Proteus* species, methicillin-resistant *Staphylococcus aureus*, enterococci, and *Candida* species. (Solomkin, et al., 2010) For healthcare-associated infections, complex multidrug regimens are recommended because adequate empiric therapy appears to be important in determining postoperative complications and mortality (Montravers, et al., 1996). In the first month of life the most common causes of cIAI are necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (Rauh, Lehane, Sieren, & Neff, 2023). NEC affects 7% of infants with birth weights between 500 and 1500 g and carries an estimated mortality rate between 20-30% (Neu & Walker, 2011). Acute appendicitis in neonates is rare. However, the perforation rate of neonatal appendicitis is high in the setting of a thin-viscus wall and relative inelasticity of the appendiceal wall due to the large amount of lymphoid tissue. (Stiefel, Stallmach, & Sacher, 1998) Conversely, among infants and older children, the most common cause of cIAI is ruptured appendicitis (Newman, et al., 2009). Selection of antibacterial therapy for cIAI should be based on considerations of the origin of infection (community vs health care), severity of illness, and safety of the antimicrobial agents in specific pediatric age groups (Solomkin, et al., 2010).

Infants with UTIs often present with fever, poor feeding, vomiting, diarrhea, or lethargy. More than 50% of premature infants with UTI additionally present with respiratory symptoms

including apnea, hypoxia, or tachypnea. The incidence of UTI is highest among uncircumcised boys or those with anatomical abnormalities, most often vesicoureteral reflux (Arshad & Seed, 2015). The presence of pyuria and bacteriuria is needed for the diagnosis of a UTI. The most common bacterial etiology for neonatal UTI, similar to other age groups, is *E. coli*. However, the overall burden of disease attributed to *E. coli* may be lower in the neonatal age group compared with other age groups (about 50% of all positive cultures in neonates compared with up to 80% in older age groups). Male infants with vesicoureteral reflux are especially likely to present with UTIs caused by other gram-negative pathogens including *Klebsiella pneumonia*e, *Proteus* species, and *Enterobacter* species. (Arshad & Seed, 2015) Due to the association with anatomic abnormalities and the risk of long-term renal insufficiency, all UTIs in neonates and infants are considered cUTI (Chang & Shortliffe, 2006). Treatment with antibacterials should be adjusted according to sensitivity testing of the isolated uropathogen(s) (Roberts, et al., 2016).

HABP and VABP are closely related infections of the lung parenchyma involving similar pathogens and are subcategories of nosocomial pneumonia (NP). HABP is inflammation of the tissue of one or both lungs caused by an infection that occurs during a hospital stay (i.e., 48 hours or more after hospital admission) or within 7 days after hospital discharge and VABP occurs following 48 hours of intubation. Symptoms of HABP or VABP include fever, leukopenia, or leukocytosis; new onset of purulent sputum, or increased respiratory secretions, or increased suctioning requirements; new onset or worsening cough, dyspnea, or tachypnea, rales, or bronchial breath sounds; worsening gas exchange, increased oxygen requirements or increased ventilator demand (CDC NHSN, 2023).

In hospitalized children, HABP has an incidence of 12%. VABP has an incidence of 4.3 cases per 1000 ventilator-days in children under 120 days old. The most common bacterial etiology of HABP or VABP for children < 28 days is *S. aureus* but gram-negatives including *E. coli, K. pneumoniae, Haemophilus influenzae*, and *Enterobacter* species are seen in more than half of HABP/VABP infections in children < 28 days. PsA is the most commonly identified organism in the 120 days to 18-year-old age group, cultured in 44% of HABP/VABP cases. PsA remains prevalent in the < 120-day age group, being cultured in 22% of children, neonates and infants less than 120 days (Ericson, et al., 2020). Antibacterial therapy should be based on microbiology culture results.

2.2. Analysis of Current Treatment Options

Table 1. Therapeutic Options for Gram-Negative cIAI; cUTI; or HABP/VABP

Generic Name	Trade Name	Relevant Indication	Approved Age Range for Indication	Other Comments
Cephalosporins (Parenteral 2nd, 3rd, and 4th Generation)				
Cefotetan	Cefotan	Intra-abdominal infection; UTI; LRTI;	Adults only	Use of 2nd and 3rd generation cephalosporins has declined with emergence of multi-drug resistant gram-negative bacilli
Cefoxitin	Mefoxin	cIAI; UTI; LRTI	≥ 3 months	
Cefuroxime sodium	Zinacef	UTI; LRTI	≥ 3 months	
Cefotaxime	Claforan	Intra-abdominal infections; Genitourinary tract infections; LRTI	All ages	
Ceftriaxone	Rocephin	Intra-abdominal infection; cUTI; LRTI	All ages. Contraindicated in premature neonates and hyperbilirubinemic neonates	
Ceftazidime	Fortaz, Tazicef	Intra-abdominal infections including peritonitis; cUTI; LRTI	All ages	
Cefepime	Maxipime	cIAI; cUTI; MSP	≥ 2 months	
Cefiderocol	Fetroja	cUTI; HABP/VABP	Adults only	Approved for use in adults only
β-Lactam/β-Lactamase Inhibitor Parenteral Combinations				
Ceftolozane-tazobactam	Zerbaxa	cIAI; cUTI; HABP/VABP	All ages	
Meropenem-vaborbactam	Vabomere	cUTI	Adults only	
Imipenem-cilastatin-relebactam	Recarbrio	cIAI; cUTI; HABP/VABP	Adults only	
Piperacillin and tazobactam	Zosyn	cIAI; NP	≥ 2 months	
Carbapenems				
Imipenem-cilastatin	Primaxin	Intra-abdominal infection; cUTI; LRTI	All ages	
Ertapenem	Invanz	cIAI; cUTI; CAP	≥ 3 months	
Meropenem	Merrem	cIAI	All ages	
Fluoroquinolones				
Ciprofloxacin	Cipro	cUTI NP	≥ 1 year[a] Adults only	Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy.
Levofloxacin	Levaquin	cUTI; NP	Adults only	
Moxifloxacin	Avelox	cIAI; CAP	Adults only	

Generic Name	Trade Name	Relevant Indication	Approved Age Range for Indication	Other Comments
Monobactams				
Aztreonam	Azactam	Intra-abdominal infections including peritonitis; cUTI; LRTI	≥ 9 months	Although used in patients with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime
Aminoglycosides				
Gentamicin sulfate		SI	All ages	Risk of nephrotoxicity and ototoxicity. Indicated only for serious bacterial infections.
Amikacin sulfate		SI	All ages	
		Used off-label for multidrug resistant HABP/VABP		
Tobramycin sulfate		Intra-abdominal infections including peritonitis; cUTI; LRTI	All ages	
Plazomicin	Zemdri	cUTI including pyelonephritis	Adults only	Risk of nephrotoxicity and ototoxicity.
Tetracyclines				
Tigecycline	Tygacil	cIAI; CAP	Adults only	*Pseudomonas aeruginosa* is intrinsically resistant to tigecycline. Pediatric trials were not conducted because of the higher risk of mortality seen in adult trials.
Eravacycline	Xerava	cIAI	≥ 8 years	NOT indicated for cUTI
Sulfonamide				
Trimethoprim-Sulfamethoxazole	Bactrim	Severe UTI (IV only); UTI (oral)	≥ 2 months	Contraindicated <2 months of age
Polymyxins				
Polymyxin B Sulfate		SI	All ages	Some gram-negatives are intrinsically resistant (e.g., *Proteus* spp; *Providencia* spp; *Burkholderia cepacia*); safety risks including nephrotoxicity and rare but serious neurotoxicity. Indicated when less potentially toxic drugs are ineffective or contraindicated.
Colistimethate	Coli-mycin M	SI	All ages	

Source: Adapted from Dr. Gillian Taormina's NDA 206494 Supplements 005 and 006 review on March 13, 2019 (Tables 2 and 3) and Dr. Elizabeth Story-Roller's NDA 206494 Supplement 11 review on December 19, 2022 (Table 1).
[a] Although effective in clinical trials, ciprofloxacin tablets are not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to controls, including reactions related to joints and/or surrounding tissues.
Abbreviations: CAP Community-acquired pneumonia; cIAI complicated intrabdominal infections; cUTI Complicated urinary tract infections; HABP Hospital-acquired bacterial pneumonia; LRTI Lower respiratory tract infection; MSP Moderate to Severe Pneumonia; NP Nosocomial pneumonia; RTI Respiratory tract infections; SI Serious Infections; UTI urinary tract infection; VABP Ventilator-associated bacterial pneumonia

There are limited treatment guidelines for children with cIAI, cUTI, or HABP/VABP. The 2010 IDSA treatment guidelines for adults and children with cIAI are archived, with new guidelines in-development. The American Academy of Pediatrics treatment guidelines for UTI in febrile infants and children apply to the 2-to-24-month age group. IDSA Guidelines for the treatment of HABP/VABP focus on adults.

Not all of the above listed antibacterial drugs in Table 1 are approved for use in pediatric patients. Treatment can be either empiric or directed based on the results of microbiologic studies. Patients assessed as being at low risk for antibacterial resistance are recommended for initial empiric therapy with a narrow-spectrum antibacterial, whereas high-risk patients will require broader therapy with a combination of different classes of antibacterials. For empiric therapy, the above drugs may be given in combination with antibacterial drugs active against gram-positive pathogens, such as vancomycin or linezolid for methicillin-resistant *S. aureus*.

Aztreonam is recommended in patients with severe β-lactam allergies (but is only approved for use in patients ≥ 9 months). There are, however, concerns about allergic cross-reactivity with aztreonam and ceftazidime. Antibacterials such as aminoglycosides and colistin are not recommended, due to their adverse event profiles, unless alternative adequate gram-negative active antibacterials are unavailable.

Treatment options for pediatric patients with cIAI, cUTI, or HABP/VABP caused by MDR pathogens are limited. AVYCAZ has demonstrated *in vitro* activity against Enterobacterales in the presence of some beta-lactamases and ESBLs of the following groups: TEM, SHV, CTX-M, *Klebsiella* pneumoniae carbapenemase (KPCs), AmpC, and certain oxacillinases (OXA). AVYCAZ has also demonstrated *in vitro* activity against *PsA* in the presence of some AmpC beta-lactamases, and certain strains lacking outer membrane porin D (OprD). AVYCAZ is not active against bacteria that produce metallo-beta lactamases and may not have activity against gram-negative bacteria that overexpress efflux pumps or have porin mutations. The approval of AVYCAZ for treatment of cIAI, cUTI, or HABP/VABP in neonates and infants from birth (gestational age ≥ 31 weeks) to 3 months of age could help fulfill an unmet need.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

AVYCAZ is an antibacterial fixed dose combination of ceftazidime, a third-generation cephalosporin, and avibactam, a non-β-lactam β-lactamase inhibitor at a ratio of 4:1. AVYCAZ was initially approved on February 25, 2015, for the treatment of adults with cUTI, including pyelonephritis, and cIAI in combination with metronidazole 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 limitation of use statements. Two subsequent efficacy supplements provided clinical trial data with statistical inference testing to support the removal of the limitation of use statements. The adult efficacy supplement for cIAI was approved on June 22, 2016 (S-002) and cUTI on January 26, 2017 (S-003). The efficacy supplement for HABP/VABP in adults was approved on February 1, 2018 (S-004).

This is the fourth AVYCAZ pediatric efficacy supplement to address Pediatric Research Equity Act (PREA) post-marketing requirements (PMR). The current efficacy supplement (S-012) proposes to extend the approved indications for treatment of cIAI, cUTI, and HABP/VABP to infants and neonates < 3 months and is submitted to fulfill PMR 2862-3. Prior AVYCAZ pediatric efficacy supplements were approved on:

1. March 14, 2019, for the indications of cUTI (S-005) and cIAI (S-006) in pediatric patients ≥ 3 months of age - PMR 2862-1 (cUTI) and 2862-2 (cIAI).
2. December 20, 2022, for the indication of HABP/VABP (S-011) in pediatric patients ≥ 3 months of age - PMR 2862-6.

3.2. Summary of Presubmission/Submission Regulatory Activity

Key regulatory interactions and proceedings relevant to AVYCAZ pediatric development:

- February 25, 2015: Approval of AVYCAZ for the treatment of cIAI, in combination with metronidazole, and cUTI, including pyelonephritis, in adult patients who have limited or no alternative treatment options. PREA PMR 2862-03 was included to conduct a study to evaluate the pharmacokinetics (PK), safety and tolerability of AVYCAZ in infants and neonates < 3 months with late-onset sepsis.
- February 1, 2018: Approval of AVYCAZ for the treatment of patients 18 years or older with HABP/VABP caused by the following susceptible gram-negative microorganisms: *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Escherichia coli*, *Serratia marcescens*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* (S-004).
- February 20, 2018: Applicant submitted a proposal to decrease the number of subjects in Part B of Study C3591024 from 24 to 12 by reducing the 3 cohorts to 4 subjects each, rather than 8 subjects per cohort. The Applicant proposed to keep the number of subjects in Part A the same, at 24 subjects divided into 3 cohorts. FDA did not agree to this proposal but recommended the Applicant document all the efforts made in an attempt to enroll patients

and that the Applicant's efforts to satisfy the PMR will be taken into consideration when making a final decision on the adequacy of the number of subjects enrolled. The European Medicines Agency (EMA) accepted the proposal to reduce the number of subjects in Part B of the study to 12 subjects.

- June 28, 2018: The original protocol for Study C3591024 was submitted to IND 101307, titled, "A Phase 2a, 2-part, open-label, non-randomized, multicenter, single and multiple dose study to evaluate pharmacokinetics, safety and tolerability of ceftazidime and avibactam in neonates and infants from birth to less than 3 months of age with suspected or confirmed infections due to gram-negative pathogens requiring intravenous antibiotic treatment." The study was expected to begin in November 2018.
- September 14, 2018: Submission of pediatric efficacy supplements 5 and 6 including data from two pediatric phase 2 studies [D4280C00016 (PMR #2862-1) and D4280C00015 (PMR #2862-2)] providing evidence for the efficacy and safety of AVYCAZ in the treatment of pediatric patients ≥ 3 months of age with either cUTI, including pyelonephritis, or cIAI, respectively. These efficacy supplements were approved on March 14, 2019.
- July 10, 2019: Protocol Amendment 1 for Study C3591024 which included clarification of the eligibility criteria that under 3 months of age is defined as < 89 days.
- September 16, 2019: Applicant submitted a pediatric deferral extension request for Study C3591024 to account for delays in study initiation and anticipated challenges with recruitment. This pediatric deferral extension was granted on October 29, 2019, with the revised timeline for completion of Study C3591024 updated to December 2021 with a Final Report submission due date of June 2022.
- January 15, 2020: First subject enrolled in Study C3591024.
- March 23, 2020: Study C3591024 enrollment paused at all sites due to the COVID-19 pandemic. One subject had completed the study prior to the enrollment pause and a second subject continued the study per protocol and completed the study during the enrollment pause.
- April 13, 2020: Enrollment pause for Study C3591024 was extended.
- April 30, 2020: Enrollment in Study C3591024 was restarted globally on a site-by-site basis.
- September 30, 2021: Applicant submitted a pediatric deferral extension request for Study C3591024 due to delays in conducting the study and anticipated challenges with recruitment. This pediatric deferral extension was granted on November 04, 2021; with a revised timeline for study completion date updated to December 2022 with a Final Report submission due date of June 2023.
- June 22, 2022: Submission of pediatric efficacy supplement (S-011) including limited data from a single dose pediatric PK study in patients with HABP/VABP (C3591025, PMR #2862-6) to support a proposed indication for use of AVYCAZ in pediatric patients aged 3 months to < 18 years with HABP/VABP.
- August 29, 2022: Applicant submitted a Type C Meeting – Written Response Only request to obtain agreement from the Division that the clinical and PK data package from Study

C3591024 (which was anticipated to be available by the study completion deadline of December 2022) would be sufficient to fulfill PMR 2862-3 and to support the filing of an sNDA seeking approval of AVYCAZ for the treatment of patients aged birth to < 3 months across indications.

- September 23, 2022: The Applicant proposed to submit clinical and PK data from at least 44 evaluable patients ages birth to < 3 months, as opposed to the original plan to provide data for 48 evaluable subjects. The Applicant had completed enrollment in all cohorts except Part B Cohort 2 (full term neonates from birth to ≤ 28 days receiving AVYCAZ), where 5 subjects had been enrolled and were evaluable for safety, 4 of whom were also evaluable for PK. The study had recruitment challenges for Cohort 2B given most of the study investigators were neonatologists who do not manage full-term infants. Feedback the Applicant received from investigators also indicated that the parents of full-term infants may be less inclined to join a clinical study than parents of premature infants, who have more of an established relationship with the hospital staff. Measures to continue to encourage recruitment including refresher investigator meetings implemented by the Applicant. On November 07, 2022, FDA provided responses stating that they expected that 44 evaluable subjects with clinical and PK data would be adequate to support review of the sNDA package but noted that it was premature to agree whether the clinical and PK data package for Study C3591024 would be sufficient to fulfill PMR 2862-3 as this determination would be a review issue.
- November 22, 2022: The Applicant submitted the study termination letter for Study C3591024 to IND 101307, and the study was terminated on December 30, 2022.
- December 20, 2022: Pediatric efficacy supplement (S-011) was approved in fulfillment of PMR 2862-6. This extended the indication for treatment of HABP/VABP in pediatric patients to age 3 months to < 18 years.
- January 26, 2023: The Applicant submitted a meeting request for a pre-sNDA Type C Meeting-Written Response Only meeting to discuss the sNDA submission plan for consideration of fulfillment of PMR 2862-3 based on data from Study C3591024.
- March 29, 2023: The Applicant submitted a deferral extension request for PREA PMR 2862-3 to revise the final report submission timeline for Study C3591024. The Applicant's development partner, Pfizer, was informed of delays in the processing time for PK samples occurring at their vendor site, (b) (4) which resulted in a delay in receiving final PK data.
- April 07, 2023: FDA provided the written responses for the pre-sNDA Type C Meeting. FDA agreed that the data from Study C3591024 along with supporting safety and efficacy data from prior adult and pediatric studies in patients with cIAI, cUTI, and HABP/VABP could be used to support a proposed extension of these indications to patients from birth to less than 3 months. FDA did not agree with the Applicant's proposal to (b) (4) The deferral extension was granted

because of delays in collecting and compiling the study data with a final report submission extension date of September 2023.

- July 28, 2023: The Applicant submitted pediatric efficacy supplement (S-012) with data from a single pediatric PK and safety study (C3591024, PMR 2862-3) to support extension of the approved AVYCAZ indications for treatment cIAI, cUTI, and HABP/VABP to pediatric patients from birth to less than 3 months of age.

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

4.1. Office of Study Integrity and Surveillance (OSIS)

Study C3591024 clinical site 1029 enrolled 11/21 (52.4%) of the subjects in the multiple-dose (Part B) part of the study and was noted to have a large number of protocol deviations categorized as "important" (128 in total). Evaluation of the types of deviations showed that 5/11 (45.5%) of the subjects enrolled at Site 1029 had protocol deviations related to obtaining informed consent. Given that this clinical site enrolled a large proportion of the subjects in the study, the clinical review team requested inspection of this clinical site.

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of site 1029 which was performed by the Office of Regulatory Affairs (ORA) December 4-7, 2023. No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. However, three items were discussed with the study site management on inspection close-out:

- One subject ([(b) (6)]) enrolled in Cohort 3 (pre-term neonates) did not meet the protocol-specified eligibility criteria for this cohort since the subject's postnatal age (PNA) was 37 days and the site investigator incorrectly used the corrected age (PNA – number of weeks born before 40 weeks gestation) to determine eligibility.
  - The impact of the misclassification of this subject was minimal since the review team identified this subject in the analysis and agreed with the use of the 25 mg/kg CAZ-AVI dosage for pre-term infants with a corrected age of ≤ 28 days in the dosing recommendations (see Section 6.2.1).
- One subject ([(b) (6)]) experienced a vomiting episode that was not included as an adverse event in the study report. The ORA inspector could not verify whether this event was reported on the case report form.
  - The review team verified that vomiting was reported as an adverse event on the case report form for this subject and was included in the safety analyses (see Section 8.2.4).
- The ORA inspector's review of the interactive voice response system (IVRS) identified one vial of study treatment administered to a subject ([(b) (6)]) that was not dispensed per the IVRS. However, the inspector was able to verify the vials dispensed in the drug accountability logs so there was no impact on data reliability or subject safety.

4.2. Product Quality

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. Clinical Microbiology

Ceftazidime-avibactam is a combination product of a third-generation parenteral cephalosporin and non-β-lactam β-lactamase inhibitor, respectively. A comprehensive assessment of the clinical microbiology information for ceftazidime-avibactam was provided in the original NDA (see Dr. Avery Goodwin's clinical microbiology review dated 1/20/2015).

Study C3591024 evaluated the PK, safety and tolerability of ceftazidime-avibactam in neonates and young infants aged birth to < 3 months. The study design and results are described elsewhere in the review (see Section 8). The most prevalent gram-negative isolate was *Escherichia coli* (6 subjects), 1 subject each had *Citrobacter koseri*, *Enterobacter cloacae* complex, *Klebsiella oxytoca* and *Klebsiella pneumoniae*. Table 2 shows that the gram-negative pathogens identified in 10 subjects were susceptible to ceftazidime-avibactam with MICs ranging from 0.12/4 mg/L to 1/4 mg/L. The one subject that had clinical failure was infected with an *Enterobacter cloacae* complex isolate and the isolate was presumed persistent at TOC.

Table 2. Ceftazidime-Avibactam Activity Against Isolates Collected in Subjects From Study C2491024

Baseline Isolate	Number of Subjects	Ceftazidime-Avibactam MIC (range in mg/L)
Escherichia coli	6	0.06/4 – 0.5/5
Klebsiella oxytoca	1	0.12/4
Citrobacter koseri	1	0.25/4
Enterobacter cloacae complex	1	0.5/4
Klebsiella pneumoniae	1	1/4

Source: Study C35910124 CSR.

Overall, isolates in neonates and young infants aged birth to < 3 months showed similar ceftazidime-avibactam MICs when compared with isolates obtained from pediatric subjects (> 3 months of age) and adults (Study Report# CAZ-AVI neonatal surveillance report 31-January-2023).

There are no revisions to the current approved labeling with respect to clinical microbiology.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data were submitted with the current sNDA. The reader is referred to Drs. Wendelyn Schmidt and Armand Balboni's review dated 02/18/2015 of the nonclinical pharmacology/toxicology data in the original NDA submission. Additionally, Section 5: Nonclinical Pharmacology/Toxicology of the NDA Multi-disciplinary Review and Evaluation for NDA 206494 (pediatric efficacy supplements 005 and 006) includes reviews of range-finding and definitive juvenile toxicology studies in rats.

6. Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology information contained within the current sNDA supports the approval of AVYCAZ® (ceftazidime-avibactam) for the treatment of complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in neonates (i.e., full-term and pre-term neonates with gestational age (GA) ≥ 31 weeks) to infants < 3 months of age. See Table 3 for a summary of the clinical pharmacology-related recommendations and comments on key review issues.

Table 3. Summary of OCP Recommendations and Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness and safety	**Effectiveness** Pivotal evidence of effectiveness for the Applicant's proposed ceftazidime-avibactam (CAZ-AVI) dosage for the treatment of neonates (i.e., full-term and pre-term neonates with GA ≥31 weeks) to infants < 3 months of age with cUTI (including acute pyelonephritis), cIAI, and HABP/VABP is based on the extrapolation of effectiveness from the approved CAZ-AVI dosage for the same indications in adult patients. This extrapolation of effectiveness is predicated on the achievement of similar CAZ and AVI exposures in neonates and infants (< 3 months of age) with cUTI, cIAI, and HABP/VABP as compared to adult patients with the same infection types. Specifically: • Interquartile ranges for simulated CAZ-AVI $C_{max,ss}$ and $AUC_{ss,0-24h}$ for neonates and infants (< 3 months of age) are comparable or lower than the corresponding adult ranges (across all indications), except for pre-term neonates with GA of 26 to 30 weeks, where the interquartile range for CAZ $AUC_{ss,0-24h}$ exceeds the adult reference ranges. Notably, in the age groups with lower CAZ-AVI $C_{max,ss}$ and/or $AUC_{ss,0-24h}$, the interquartile range for $C_{min,ss}$ is either comparable or exceeds the corresponding adult ranges. Because the PK-PD indices for CAZ and AVI are %*f*T>MIC and %*f*T>C_T, respectively, and that C_{min} better correlates with these indices than either C_{max} or AUC, these exposures are expected to be efficacious (as evidenced by the comparable joint probability of target attainment (PTA) results in these patients and adults). Refer to the information on joint PTA below for details.

Review Issue	Recommendations and Comments
	• In pre-term neonates with GA 26 to 30 weeks, the predicted interquartile range of CAZ-AVI $C_{max,ss}$ (which is comparable to the adult reference range) and $AUC_{ss,0-24h}$ (where the range for CAZ exceeds the adult ranges, and mean CAZ $AUC_{ss,0-24h}$ exposures are 57-69% higher than corresponding adult values) are expected to be efficacious. However, there is insufficient information to ascertain the safety of these higher exposures (see the Safety subheading below for the safety-related assessment and Sections 6.2.1 and 15.4.3 for additional details). Additionally, supportive evidence is provided by: 1. Findings from joint PTA assessment showing that the Applicant's proposed CAZ-AVI dosage for neonates and infants (< 3 months of age) with cUTI, cIAI, and HABP/VABP yields joint PTA estimates above 90% at the current breakpoint of 8 µg/mL for susceptible pathogens. See Sections 6.2.1 and 15.4.3 for additional details. 2. Efficacy data obtained from neonates (full-term and pre-term with GA ≥ 31 weeks and infants (< 3 months of age) administered the proposed dosage regimens in Study C3591024, a Phase 2a safety, efficacy, and PK trial (See Section 8.1). **Safety** Evidence of safety is based on findings from Study C3591024 See Section 8.2 for details on the safety evaluation). Further evidence of safety is based on comparison of CAZ and AVI exposures in neonates and infants (< 3 months of age) receiving the Applicant's proposed dosage regimen and adult patients receiving the approved dosage for the same indications. As noted above, mean CAZ-AVI exposures are either lower or comparable for all age cohorts except for pre-term neonates with GA of 26-30 weeks, for whom the predicted mean CAZ $AUC_{ss,0-24h}$ exposures are 57-69% higher than the corresponding adult mean values. Given the higher predicted CAZ $AUC_{ss,0-24h}$ and the lack of clinical safety data in these patients, the review team recommends limiting the neonatal dosage regimen to full-term and pre-term neonates with GA ≥ 31 weeks in alignment with the demographics for Study C3591024. See Section 6.2.1 for details on the exposure comparison. In pre-term infants (defined as GA < 37 weeks), a corrected age threshold of 28 days was used to inform dosing in Study C3591024. Therefore, the review team recommends specifying the applicable age terminology for pre-term infants (as shown in dosing Table 4) to maintain consistency with the age demographics of the clinical trial population. See Section 6.2.1 for details on how the clinical trial population demographics were used to define the age cutoffs for dosing.

Review Issue	Recommendations and Comments
General dosing instructions	Table 4 shows the recommended dosing regimen of CAZ-AVI in neonates (i.e., full-term and pre-term neonates with gestational age ≥ 31 weeks) and infants < 3 months of age without renal impairment. All doses are administered as a 2 h infusion with a recommended treatment duration of 7-14 days. **Table 4. Recommended Dosing Regimen of Ceftazidime-Avibactam in Neonates and Infants Without Renal Impairment** **Age Range** / **Dosage** Less than or equal to 28 days[a] with GA 31 weeks and older / 20 mg/kg CAZ and 5 mg/kg AVI every 8 h Greater than 28 days[b] to less than 3 months / 30 mg/kg CAZ and 7.5 mg/kg AVI every 8 h [a] Includes full-term infants with PNA > 28 days and pre-term infants with corrected age > 28 days. Corrected age is calculated by subtracting the number of weeks born before 40 weeks of gestation from the postnatal age. [b] Includes neonates PNA ≤ 28 days and pre-term infants with corrected age ≤ 28 days. Abbreviations: GA=gestational age, PNA=postnatal age.
Dosing in patient subgroups (intrinsic and extrinsic factors)	There is insufficient information to guide dosing in infants and neonates with renal impairment.
Labeling	The Applicant's proposed labeling was reviewed, and the review team conveyed specific recommendations to the Applicant. See Labeling Recommendations in Section 11 for additional details.

Source: Generated by the FDA review team.

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness for the proposed CAZ-AVI dosage in neonates (i.e., full-term and pre-term neonates with GA ≥ 31 weeks) and infants (< 3 months of age) with cUTI (including acute pyelonephritis), cIAI, and HABP/VABP. The program is comprised of: (1) Study C3591024, a phase 2a, open-label, single and multiple-dose PK, safety and tolerability study in hospitalized infants < 3 months and neonates with suspected or confirmed infections caused by gram-negative pathogens; (2) CAZ-AVI population PK analyses; and (3) CAZ-AVI joint PTA analysis.

The evidence of effectiveness for the proposed CAZ-AVI dosing regimen in neonatal (i.e., full-term and pre-term neonates with GA ≥ 31 weeks) and infant (< 3 months of age) patients with cUTI, cIAI, and HABP/VABP is based on extrapolation of effectiveness from the approved CAZ-AVI dosing regimen for adult patients under the same indications. Because all three infection types are pathophysiologically similar in adults and pediatrics, the efficacious CAZ-AVI exposures in adults are also expected to be effective across the entire pediatric population. Population PK analyses demonstrate that the simulated steady state CAZ-AVI exposures resulting from the proposed dosing regimens in neonates (full-term and pre-term neonates

with GA ≥ 31 weeks) and infants (< 3 months of age) are reasonably similar to the efficacious exposures in adults, thus enabling the extrapolation of effectiveness from adults to these pediatric patients. Additionally, supportive evidence of effectiveness for the proposed dosing regimen is provided by the PTA results for CAZ-AVI, which are comparable between adults (receiving the currently approved CAZ-AVI dosage) and the proposed pediatric population (receiving the Applicant proposed CAZ-AVI dosage in this submission) (See Section 15.4.3 for additional details).

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Yes, the Applicant's proposed dosing regimens (summarized in Table 5) for neonates (full-term and pre-term neonates with GA ≥ 31 weeks) and infants (< 3 months of age) with normal renal function are acceptable primarily based on comparison of exposures between these pediatric subpopulations and adults with the same infections. Additional supportive evidence for the proposed regimens is provided by the results of joint CAZ-AVI PTA analysis. A review of the supportive clinical pharmacology information for the proposed dosing regimens is summarized below with additional details under Sections 15.4.2 and 15.4.3.

To support the proposed indications, the Applicant conducted Study C3591024, a phase 2a, single and multiple-dose PK, safety and tolerability study in hospitalized neonates and infants < 3 months with suspected or confirmed infections caused by Gram-negative pathogens. Subjects were enrolled across 3 age cohorts (N=8/cohort) and administered either single or multiple doses of CAZ-AVI as a 2 hour (h) IV infusion based on the recommended dosing regimens summarized in Table 5. The combined demographic information for participants in the single- and multiple-dose portions of the study is also summarized (per cohort) in Table 5. As noted in the table, the Applicant used discrepant age terminology (i.e., corrected age versus postnatal age (PNA)) to facilitate enrollment of patients with GA < 37 weeks into Cohorts 1 and 3 of Study C3591024. Specifically, within the clinical trial population:

- Cohort 1, which planned to enroll full-term infants (i.e., GA ≥ 37 weeks) with PNA > 28 days, also enrolled 2 pre-term infants (i.e., GA < 37 weeks) due to the use of their respective corrected age (defined as the difference between PNA and number of weeks born before 40 weeks gestation) > 28 days at the time of enrollment.
- Cohort 3, which was expected to enroll pre-term neonates with GA 26 to < 37 weeks and PNA ≤ 28 days, enrolled pre-term neonates with GA ≥ 31 weeks and PNA in the range of 2 – 37 days. With the exception of 1 subject with PNA of 37 days, all others in this Cohort had PNA 2 – 22 days.

To reconcile this difference in protocol-specified age groups and the ultimate age range of enrolled subjects, the review team recommended use of a corrected age threshold of 28 days to inform dose eligibility in pre-term infants (see Table 4 above). Thus, for all instances in this review describing the recommended dosage regimen, the use of corrected age is implied for pre-term infants.

Table 5. Summary of Dosage and Selected Demographic Information From Study C3591024

Age Cohort	Dose[a]	N	Observed GA[b] Range (Weeks)	PNA[c] (Days)	Observed Weight (kg) Median (Min, Max)	Sex Male (%)
Infants 28 days[d] to < 3 months)	30 mg/kg CAZ and 7.5 mg/kg AVI	17	5.3 – 41	5 – 89	4.27 2.9, 6.4)	9 52.9)
Full-term neonates (GA[b] ≥ 37 weeks) and PNA ≤ 28 days	20 mg/kg CAZ and 5 mg/kg AVI	13 3	37 to 41.3 3	5 – 28	2.88 2.2, 4.0)	8 61.5)
Pre-term neonates (GA[b] 26 to < 37 weeks and PNA ≤ 28 days	20 mg/kg CAZ and 5 mg/kg AVI	16	31 – 36	2 – 37	1.81 1.3, 2.6)	4 25)

Source: Compiled by reviewer from Study Report C3591024 and Population PK Analysis Report.
[a.] Administered every 8 h in the multiple-dose portion of the study.
[b.] GA=gestational age
[c.] PNA=postnatal age
[d.] Includes full-term infants (GA ≥ 37 weeks with PNA > 28 days and pre-term infants with corrected age > 28 days. Corrected age=PNA - number of weeks born before 40 weeks of gestation

1) Exposures in Neonates and Infants (< 3 Months of Age) as Compared to Adult Patients

Previously developed CAZ and AVI population PK models (which were informed by existing PK data in adults and pediatric patients 3 months to < 18 years of age) were updated with PK data obtained from Study C3591024. The updated model was then used to estimate post-hoc steady-state PK parameters for the clinical trial population (summarized in Table 6) and to simulate exposures in neonates (with GA ≥ 26 weeks) and infants (< 3 months of age) with cUTI, cIAI, and HABP/VABP administered the proposed dosing regimen. The simulated pediatric exposures (summarized in Tables 7, 8, 9 and 10) were then compared to the corresponding exposures in adults with cUTI, cIAI and HABP/VABP. A detailed discussion of exposure comparisons is provided below.

Table 6. Summary of Mean Post-Hoc PK Parameters at Steady State by Age Cohort

		Mean (%CV)	
Age Cohort	**N**	**$C_{max,ss}$ (µg/mL)**	**$AUC_{ss,0-24h}$ (µg·h/mL)**
CAZ			
Pre-Term neonates[a] (GA[b] 31 – 36 weeks)	16	50.4 (22.1)	653 35.7)
Full-Term neonates[a] (GA[b] ≥37 weeks)	12	43.6 18)	505 30
Infants >28 days to <3 months)	16	61.4 14)	626 23.8)
Adults >18 years of age	1810	74 33.9)	858 47.6)
AVI			
Pre-Term neonates (GA[b] 31 – 36 weeks)	16	9.18 95.7)	119 99.6)
Full-Term neonates (GA[b] ≥37 weeks)	12	8.4 48)	94.1 (62
Infants >28 days to <3 months)	16	12.1 (29.8)	115 35.9)
Adults >18 years of age	1831	12.8 (68.3)	141 72.2)

Source: Adapted from Table 1 of Applicant's Response to FDA's December 19th IR and Table 2 of the Applicant's Summary of Clinical Pharmacology Studies.
[a.] Chronological age ≤28 days
[b.] GA=gestational age

Exposures in Pre-Term Neonates With GA ≥ 26 to < 31 Receiving the Proposed Dosage Regimen

As shown in Table 7, in pre-term neonates (GA 26 to < 37 weeks), the predicted mean CAZ $AUC_{ss,0-24h}$ values are 20-29% higher than the corresponding adult mean values. However, post-hoc estimates of CAZ $AUC_{ss,0-24h}$ (shown in Table 6) indicate that mean exposures in this cohort are lower than the adult exposures. Given that Cohort 3 of Study C3591024 was solely comprised of pre-term neonates with GA ≥ 31 weeks, the difference between the post-hoc estimates of mean CAZ $AUC_{ss,0-24h}$ for the clinical trial population and the model-predicted exposures for this patient population may be attributed to the model's accounting for pre-term neonates down to GA ≥ 26 weeks. To explore the potential impact of younger pre-term gestational age on the predicted CAZ exposures, the Applicant was asked to provide additional analyses comparing simulated drug exposures in pre-term neonates with GA ≥ 26 weeks to 30 weeks with those in pre-term neonates with GA 31 to 36 weeks, and the corresponding adult exposures.

Table 7. Geometric Mean CAZ Exposures and Joint PTA in Simulated Patients With Normal Renal Function

		Mean	Mean (Pediatric: Adult Ratio)		
PK Parameters	Infection Type	Adults (≥18 Years of Age)	Pre-Term Neonates[a] (GA[b] 26 to <37 Weeks)	Full-Term Neonates[a] (GA[b] ≥37 Weeks)	Infants (>28 Days to <3 Months)
$C_{max,ss}$ (µg/mL)	cUTI	74.4	58.7 0.79)	42.1 0.57)	53.9 (0.72)
$C_{min,ss}$ (µg/mL)	cUTI	9.22	26.1 2.83)	12.3 1.33)	10.8 (1.17)
$AUC_{ss,0-24h}$ (µg·h/mL)	cUTI	823	990 1.20)	609 0.74)	696 0.85)
Joint PTA (%)[c]	cUTI	96.9	99.1	98.5	98.6
$C_{max,ss}$ (µg/mL)	cIAI	58.1	45.8 0.79)	33.2 0.57)	42.6 (0.73)
$C_{min,ss}$ (µg/mL)	cIAI	5.56	18.5 3.33)	8.38 1.51)	7.1 1.28)
$AUC_{ss,0-24h}$ (µg·h/mL)	cIAI	601	748 1.24)	459 0.76)	525 0.87)
Joint PTA (%)[c]	cIAI	94.8	98.5	95.2	96.4
$C_{max,ss}$ (µg/mL)	HABP/VABP	63.8	52.4 0.82)	37.3 0.58)	47.5 (0.74)
$C_{min,ss}$ (µg/mL)	HABP/VABP	7.79	24.7 3.17)	11.9 1.53)	10.7 (1.37)
$AUC_{ss,0-24h}$ (µg·h/mL)	HABP/VABP	699	903 1.29)	555 0.79)	635 0.91)
Joint PTA (%)[c]	HABP/VABP	96.3	99.1	97.8	98.6

Source: Adapted from Tables 13-15 of Applicant's Population Modeling Analysis Report.
[a.] Chronological age ≤28 days
[b.] GA=gestational age
[c.] Joint PTA assessed based on 50% *f*T>MIC of 8 µg/mL for CAZ and 50% *f*T>1 µg/mL for AVI.

Table 8. Geometric Mean AVI Exposures in Simulated Patients With Normal Renal Function

		Mean	Mean (Pediatric: Adult Ratio)		
PK Parameters	Infection Type	Adults (>18 Years of Age)	Pre-Term Neonates[a] (GA[b] 26 to <37 Weeks)	Full-Term Neonates[a] (GA[b] ≥37 Weeks)	Infants >28 Days to <3 Months)
$C_{max,ss}$ (µg/mL)	cUTI	10.1	7.22 0.71)	5.9 0.58)	7.88 0.78)
$C_{min,ss}$ (µg/mL)	cUTI	1.1	2.5 2.27)	1.44 1.31)	1.45 1.32)
$AUC_{ss,0-24h}$ (µg·h/mL)	cUTI	112	112 1)	82.1 0.73)	101 0.90)
$C_{max,ss}$ (µg/mL)	cIAI	10.3	7.47 0.73)	6.14 0.60)	8.23 0.80)
$C_{min,ss}$ (µg/mL)	cIAI	0.82	2.33 2.84)	1.31 1.60)	1.28 1.56)
$AUC_{ss,0-24h}$ (µg·h/mL)	cIAI	105	112 1.1)	82.1 0.78)	101 0.96)
$C_{max,ss}$ (µg/mL)	HABP/VABP	11	8.13 0.74)	6.76 0.61)	9.1 0.83)
$C_{min,ss}$ (µg/mL)	HABP/VABP	0.8	1.94 (2.43)	1.02 1.28)	0.95 1.19)
$AUC_{ss,0-24h}$ (µg·h/mL)	HABP/VABP	109	112 1.03)	82.1 0.75)	101 0.96)

Source: Adapted from Tables 13-15 of Applicant's Population Modeling Analysis Report.
[a.] Chronological age ≤28 days
[b.] GA=gestational age

Based on the results of these analyses (displayed in Figure 1, panels A and B for the cIAI patient population), the interquartile range of predicted AVI $AUC_{ss,24h}$ are comparable for the 2 pre-term neonate sub-cohorts (i.e., GA ≥ 26 to 30 weeks and GA ≥ 31 to 36 weeks) and adults, with mean exposures 18-26% higher in pre-term neonates with GA ≥ 26 to 30 weeks than adults (Table 10). However, for CAZ, the interquartile range (Figure 1, panels C and D) of predicted $AUC_{ss,24h}$ values for pre-term neonates with GA ≥ 26 to 30 weeks exceeds the adult reference ranges, with mean values 57-69% (Table 9) higher than the corresponding adult mean values.

Figure 1. Boxplots of $C_{max,ss}$ and $AUC_{ss,0\text{-}24h}$ for AVI (Panel A and B) and CAZ (Panels C and D) Across Age Groups in the cIAI Population

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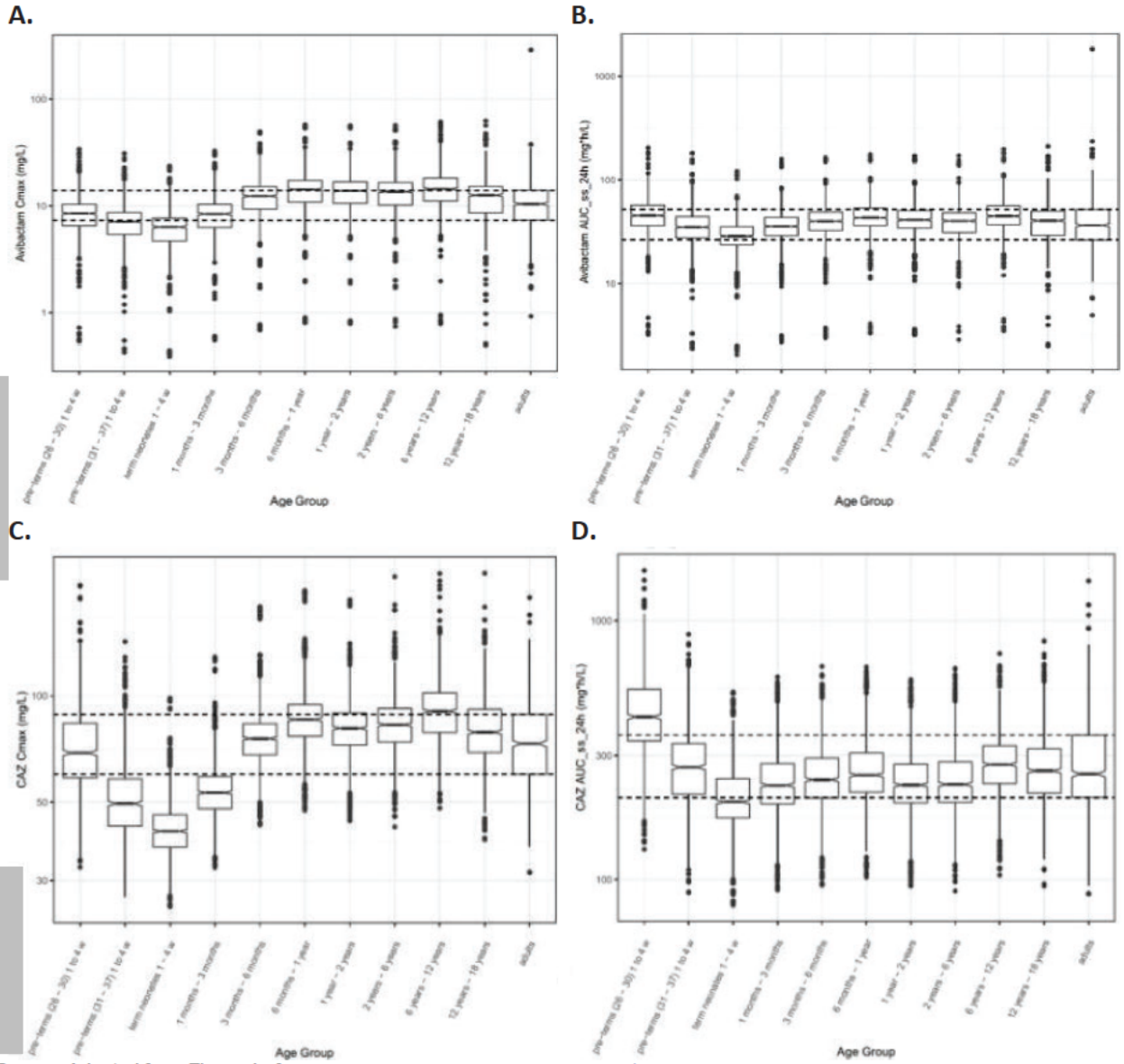

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Source: Adapted from Figure 4 of Applicant's Response to FDA's December 19th IR.

Table 9. Updated Geometric Mean CAZ Exposures and Joint PTA in Simulated Neonatal Patients and Adults With Normal Renal Function

		Mean	Mean (Pediatric: Adult Ratio)	
PK Parameters	Infection Type	Adults (≥18 Years of Age)	Pre-Term Neonates[a] (GA[b] 26 to 30 Weeks)	Pre-Term Neonates[a] (GA[b] 31 to 37 Weeks)
$C_{max,ss}$ (µg/mL)	cUTI	74.4	70.6 0.95)	50.6 0.68)
$C_{min,ss}$ (µg/mL)		9.22	38.7 4.20)	19.7 2.14)
$AUC_{ss,0-24h}$ (µg·h/mL)		823	1290 1.57	809 0.98)
Joint PTA (%)[c]		96.8	99.1	98.9
$C_{max,ss}$ (µg/mL)	cIAI	58.1	54.8 0.94)	39.7 0.68)
$C_{min,ss}$ (µg/mL)		5.56	28 5.04	13.8 2.48)
$AUC_{ss,0-24h}$ (µg·h/mL)		601	974 1.62)	611 1.02)
Joint PTA (%)[c]		95.1	99.1	98.1
$C_{max,ss}$ (µg/mL)	HABP/VABP	63.8	63.2 0.99)	45 0.71
$C_{min,ss}$ (µg/mL)		7.79	36.2 (4.64)	18.7 2.40)
$AUC_{ss,0-24h}$ (µg·h/mL)		699	1180 1.69	738 1.06)
Joint PTA (%)[c]		96.1	99.1	98.8

Source: Adapted from Tables 2-4 of Applicant's Response to FDA's December 19th IR.
[a.] Chronological age ≤28 days
[b.] GA=gestational age
[c.] Joint PTA assessed based on 50% *f*T>MIC of 8 µg/mL for CAZ and 50% *f*T>1 µg/mL for AVI.

Table 10. Updated Geometric Mean AVI Exposures in Simulated Neonatal Patients and Adults With Normal Renal Function

		Mean	Mean (Pediatric: Adult Ratio)	
PK Parameters	Infection Type	Adults (>18 Years of Age)	Pre-Term Neonates[a] (GA[b] 26 to <37 Weeks)	Pre-Term Neonates[a] (GA[b] 31 to 37 Weeks)
$C_{max,ss}$ (µg/mL)	cUTI	10.1	8.02 0.79)	6.67 0.66)
$C_{min,ss}$ (µg/mL)		1.1	3.29 2.99)	2.07 0.63)
$AUC_{ss,0-24h}$ (µg·h/mL)		112	132 1.18)	99.8 (0.89)
$C_{max,ss}$ (µg/mL)	cIAI	10.3	8.27 0.80)	6.92 0.67)
$C_{min,ss}$ (µg/mL)		0.82	3.1 3.78)	1.91 2.33)
$AUC_{ss,0-24h}$ (µg·h/mL)		105	132 1.26)	99.8 (0.95)
$C_{max,ss}$ (µg/mL)	HABP/VABP	11	8.94 0.81)	7.56 0.69)
$C_{min,ss}$ (µg/mL)		0.8	2.67 3.34)	1.56 1.95)
$AUC_{ss,0-24h}$ (µg·h/mL)		109	132 1.21)	99.8 (0.92)

Source: Adapted from Tables 2-4 of Applicant's Response to FDA's December 19th IR.
[a.] Chronological age ≤28 days
[b.] GA=gestational age

While these predicted mean CAZ $AUC_{ss,24h}$ values are comparable to the Applicant's stated exposure limits for safety (i.e., $AUC_{ss,0-24h}$ of 1213 µg·h/mL for CAZ obtained from adult patients with CrCL 51-80 mL/min/1.73m^2), the safety of these higher exposures cannot be ascertained due to the lack of clinical safety data for this GA group. Furthermore, given the lack of PK data, uncertainties in model estimates and possible inter-subject variabilities in exposure, it is unclear that actual CAZ $AUC_{ss,24h}$ values in pre-term neonates with GA ≥ 26 to 30 weeks are reasonably comparable to the referenced safety threshold. Therefore, the review team recommends limiting the proposed dosing regimen to the studied neonatal population in Study C3591024 (i.e., full-term neonates with postnatal age ≤ 28 days, and pre-term neonates with GA ≥ 31 weeks and corrected age ≤ 28 days).

Exposures in Pre-Term Neonates With GA ≥ 31 to <37 Weeks, Full-Term Neonates (GA > 37 Weeks) and Infants (> 28 Days to < 3 Months of Age) Versus Adults

The interquartile ranges (shown in Figure 1, panels A-D) and mean predicted CAZ-AVI $C_{max,ss}$ and $AUC_{ss,0-24h}$ (Tables 7, 8, 9 and 10) at the proposed CAZ-AVI dosage are either comparable or lower than the reference adult exposures for pre-term neonates with GA ≥ 31 weeks, full-term neonates (defined as GA ≥ 37 weeks) and infants (> 28 days to < 3 months of age). Nonetheless, for all 3 age groups, the predicted interquartile ranges and mean values for CAZ-AVI $C_{min,ss}$ exceed the adult reference values (Figure 2, bottom panel). Because CAZ's efficacy is dependent on the duration that drug concentrations exceed the MIC, and that C_{min} better correlates with this PK-PD index than either C_{max} or AUC, the exposures in these patients are expected to be efficacious. The efficacy of AVI is similarly governed by the duration of time that drug concentrations exceed a target value (i.e., 1 µg/mL), and as such, C_{min} better correlates with this PK-PD index than C_{max} or AUC. Therefore, the predicted AVI exposures in these patients are also expected to be efficacious. As noted above, pre-term infants (i.e., GA < 37 weeks) were dosed according to a corrected age threshold of 28 days instead of PNA. Therefore, to be consistent with the clinical trial population, the review team recommends 37.5 mg/kg CAZ-AVI dosage in pre-term infants with corrected age > 28 days, and 25 mg/kg CAZ-AVI for those with corrected age < 28 days.

Figure 2. Boxplots of $C_{min,ss}$ for AVI (Top) and CAZ (Bottom) Across Age Groups in the cIAI Population

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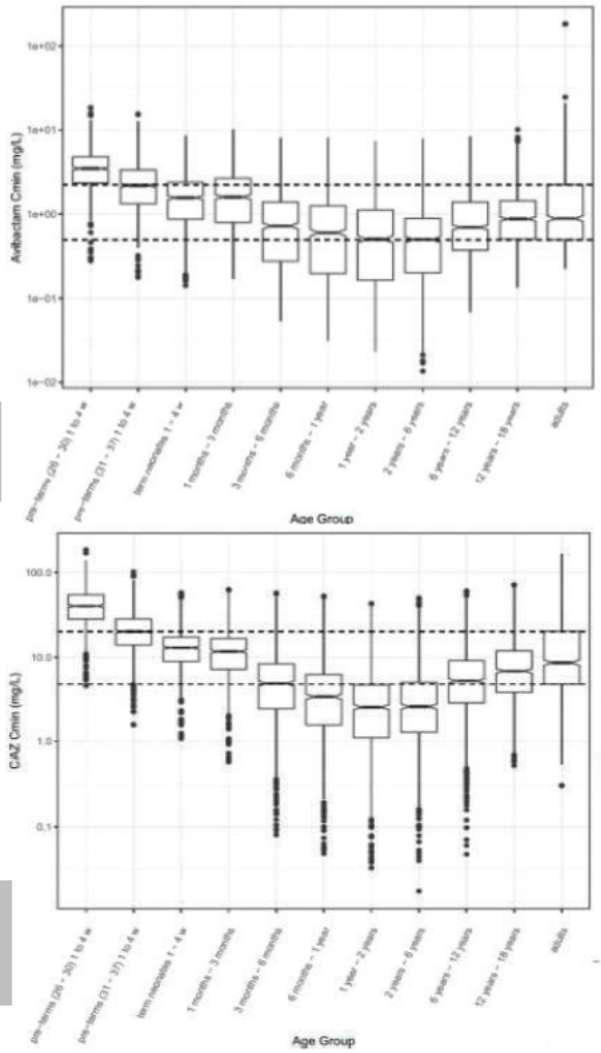

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Source: Adapted from Figure 4 of Applicant's Response to FDA's December 19th IR.

2) Joint CAZ-AVI PTA Analysis

The Applicant also conducted joint PTA analysis using the proposed dosing regimen for neonates and infants (< 3 months of age) with cUTI, cIAI, and HABP/VABP (see Section 15.4.3 for additional details). The same PK-PD targets used for adults were selected for the PTA analysis in this pediatric subpopulation (i.e., 50% *f*T>MIC for CAZ and 50% *f*T>CT of 1 µg/mL for AVI). Since the causative Gram-negative pathogens for cUTI, cIAI, and HABP/VABP and their MIC distributions are similar for adults and pediatric patients (see Section 4.3), it is reasonable to rely on the same PK-PD targets for dose selection in pediatric patients. The Applicant's joint PTA results (summarized in Table 7 and Table 9) indicate that at the proposed CAZ-AVI dosage, PTA in neonates (full-term and pre-term neonates with GA ≥ 31 weeks) and infants (< 3 months of age) exceeds 90% at the current breakpoint of 8 µg/mL for susceptible pathogens.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

The current AVYCAZ labeling provides dosage adjustments for adults and pediatric patients aged 2 years and older with renal impairment. However, for patients aged < 2 years, there is insufficient information to recommend dosage adjustments in the setting of renal impairment due to the complexity of renal maturation and the lack of PK data in this subpopulation.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Clinical safety data were reviewed from one pediatric single- and multiple-dose PK, safety, tolerability, and descriptive efficacy study enrolling newborns at least 26 weeks gestational age to infants a maximum of 89 days with suspected or confirmed infections due to gram-negative pathogens requiring intravenous (IV) antibiotic treatment (Study C3591024).

Additional pertinent pediatric and adult studies are listed in Table 48. In prior sNDA submissions, safety and efficacy data were reviewed from three prior pediatric studies in children ≥ 3 months of age: HABP/VABP (Study C3591025); cIAI (Study D4280C00015) and cUTI (Study D4280C00016). Safety and efficacy data were also reviewed from 6 prior adult studies, including four phase 3 studies: HABP/VABP (Study D4281C00001); cIAI and cUTI (Study D4280C00006); cUTI (Study D4280C00002/4); cIAI (Study D4280C00001/5) and two Phase 2 studies: cIAI (Study NXL104/2002) and cUTI (Study NXL104/2001).

Table 11. Study C3591024 to Support Safety in the Infant and Neonate Population Relevant to This sNDA

Study Identity	NCT No.	Study Design	Regimen/ Schedule/ Route	Primary Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
C3591024	NCT04126031	Phase 2, Open-label, non-randomized, multicenter, single-and multiple-dose PK, safety, and tolerability data in newborns < 3 months of age, to a gestational age of 26 weeks, with suspected or confirmed infections due to gram-negative pathogens requiring IV antibacterial treatment	Cohort 1 Infants age > 28 days to < 3 month • 30 mg/kg CAZ • 7.5 mg/kg AVI Cohort 2 Term neonates (GA ≥ 37 wk) and ≤ 28 days old) • 20 mg/kg CAZ • 5.0 mg/kg AVI Cohort 3 Pre-term neonates (GA ≥ 26 wk to < 37 wk) and ≤28 days • 20 mg/kg CAZ • 5.0 mg/kg AVI	Part A PK Part B Safety	Part A • Single-dose, 120 minutes IV infusion Part B • Multiple-dose; 120 minutes IV infusion q8H up to 14 days • Late follow-up: 28-35 days after the last IV infusion of AVYCAZ	Part A 27 subjects Part B 21 subjects	Neonates and infants from birth to < 3 months of age with suspected or confirmed infections due to gram-negative pathogens	Centers 15 study sites Countries 8 countries

Source: Adapted from Applicant's "Tabular Listing of Clinical Studies".
Abbreviations: AVI=Avibactam; CAZ=ceftazidime; GA=gestational age; IV=intravenous; mg/kg=milligram/kilogram; kg=kilogram; min=minutes; PK=pharmacokinetic$_S$); q8h=every 8 hours; wk=week

7.2. Review Strategy

Efficacy in pediatrics is extrapolated from adult studies in accordance with 21 CFR 314.55: "where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies". AVYCAZ has been granted indications for the treatment of cIAI, cUTI, and HABP/VABP in adults based on adequate and well-controlled trials, with these indications previously extended to the pediatric population from ages 3 months to less than 18 years based on efficacy extrapolation from the adult population supplemented by additional pediatric PK and safety data.

Study C3591024 was designed with the primary objective to evaluate the PK and safety of AVYCAZ in neonates and infants from birth to < 3 months of age with suspected or confirmed infections due to gram-negative pathogens. Forty-six subjects received at least a single dose in the safety population: 25 subjects received a single dose for PK evaluation and 21 subjects received multiple doses. Efficacy was evaluated as a secondary endpoint in the multiple-dose study population, including: all-cause mortality, clinical outcome, cure defined as clinical improvement and no need for further antibacterial treatment, microbiological eradication 7 to 14 days after end of therapy, and incidence of emergent infections.

Safety results are presented using descriptive statistics. Relevant reviewer commentary will be added following each analysis subsection. As this is a currently marketed product, some sections of the review template are not applicable to this review.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Studies Used to Support Efficacy

8.1.1. Study C3591024

Study Design

Study C3591024 was a 2-Part phase 2a, non-randomized, multicenter, open-label, single and multi-dose PK study to assess PK, safety, and tolerability of AVYCAZ in neonates and young infants from birth (gestational age ≥ 26 weeks) to < 3 months of age (89 days) with suspected or confirmed infections due to gram-negative pathogens requiring IV antibacterial treatment.

The primary objective of Part A was to characterize the PK of a single intravenous dose of AVYCAZ in hospitalized neonates and infants from birth to < 3 months of age. In Part A, key inclusion criteria included neonates and infants who were already receiving other IV antibacterials for treatment of suspected or confirmed bacterial infection. Subjects expected to be discharged within 24 hours after the start of AVYCAZ infusion were excluded. Secondary endpoints in Part A were safety and tolerability.

The primary objective of Part B was to evaluate the safety and tolerability of AVYCAZ for the treatment of aerobic gram-negative infections in neonates and infants from birth to < 3 months of age. Key inclusion criteria included subjects who had suspected or confirmed bacterial infection with aerobic gram-negative organisms (based on pre-defined clinical and laboratory criteria) requiring treatment with IV antibacterial drugs. Subjects with a pathogen known to be resistant to AVYCAZ or with only a gram-positive pathogen were excluded. Other key exclusion criteria were the receipt of more than 24 hours of non-study systemic antibacterial treatment for gram-negative organisms after culture and before administration of study doses of AVYCAZ; anticipated need for antibacterial therapy for longer than 14 days; or subject expected to be discharged less than 48 hours after the start of AVYCAZ infusion. Secondary endpoints were the PK profile of multiple IV doses of AVYCAZ in hospitalized neonates and infants from birth to < 3 months and the efficacy of AVYCAZ for treatment of aerobic gram-negative infection in neonates and infants from birth to < 3 months. Efficacy outcome measures included all-cause mortality; clinical outcome at End-of-Intravenous (EOIV), End-of-Treatment (EOT), Test-of-Cure (TOC), and Late Follow-Up (LFU) visits; cure defined as clinical improvement and no need for further antibacterial treatment, 7 to 14 days after end of treatment; microbiological eradication 7 to 14 days after end of treatment (micro-Intent-to-Treat analysis set); and Emergent infections.

Key study exclusion criteria for both Parts A and B included moderate or severe renal impairment defined as serum creatinine ≥ 2 times the upper limit of normal for age or urine output < 0.5 mL/kg/h (measured over at least 8 hours) or requirement for dialysis; refractory shock within 24 hours before screening that does not resolve after 60 minutes of vasopressor therapy; documented history of any hypersensitivity or allergic reaction to any β-lactam antibacterial; documented history of seizure; known *Clostridium difficile* associated diarrhea; or

the use of potent inhibitors of organic anion transports (OAT) OAT1 and/or OAT3 (e.g., probenecid, p-aminohippuric acid (PAH), or teriflunomide). Maternal use of potent OAT inhibitors was also an exclusion criterion for breastfed infants. Subjects with suspected or confirmed CNS infection were excluded because adequate penetration of AVYCAZ into the CNS has not been established.

Parts A and B were divided into 3 age cohorts:

- Cohort 1: Full term infants (gestational age ≥ 37 weeks) with chronological age > 28 days to < 3 months (< 89 days) or pre-term infants with corrected age > 28 days to < 3 months (< 89 days). Corrected age was determined by subtracting the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age was used only for determining eligibility of pre-term infants in Cohort 1.
- Cohort 2: Full term neonates (gestational age ≥ 37 weeks) from birth to ≤ 28 days.
- Cohort 3: Pre-term neonates (gestational age ≥ 26 to < 37 weeks) from birth to ≤ 28 days. Actual age (chronological age) was used for determining eligibility of pre-term neonates in Cohort 3.

Study inclusion age was defined as the "analysis age" for term infants and the corrected age for pre-term infants.

AVYCAZ (Table 12) was administered as a 120-minute infusion with an 8-hour dosing interval (for the multiple-dose Part B) for all cohorts. Cohort 1 received AVYCAZ doses of 30/7.5 mg/kg for infants > 28 days to ≤ 3 months of age (including pre-term infants with corrected age in this interval). Cohorts 2 and 3 enrolling neonates from birth to ≤ 28 days of age received AVYCAZ 20/5 mg/kg.

Table 12. AVYCAZ Doses By Cohort and Subject Age

Cohort	Age	CAZ-AVI dose	Infusion		
			Volume	Duration	Frequency
1	>28d* to <3m old	30 mg/kg CAZ 7.5 mg/kg AVI	2.5 mL/kg	120 min	q8 hr (Part B Only)
2	GA ≥37wk and ≤28d old	20 mg/kg CAZ 5.0 mg/kg AVI			
3	GA ≥26wk to <37wk and ≤28d old	20 mg/kg CAZ 5.0 mg/kg AVI			

GA = Gestational Age; d = days; hr = hours; m = month; min = minutes; wk = week.

*Includes term infants (GA ≥37 weeks) >28 days of age and pre-term infants with corrected age >28 days. Corrected age = Subtract the number of weeks born before 40 weeks of gestation from the chronological age (Engle, 2004).[3]

Source: Applicant Final Protocol for Study C3591024, Table 2.

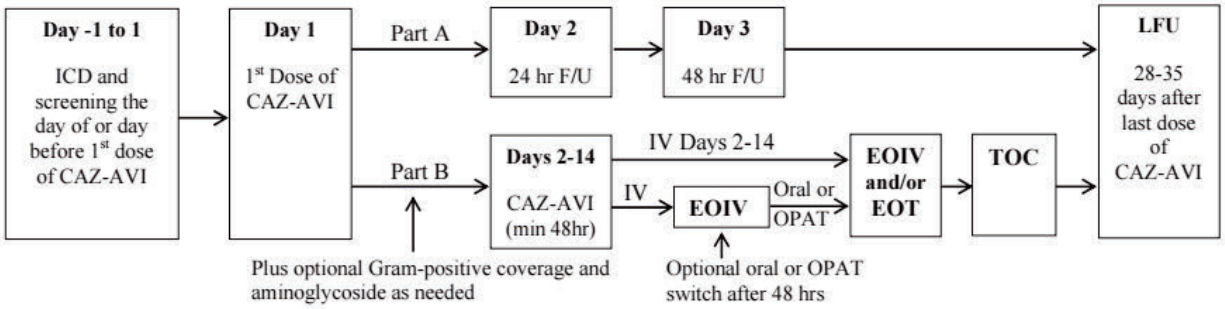
Figure 3 outlines key events for Study C3591024. In Part A, on Study Day 1 subjects received a single IV infusion of AVYCAZ over a 2-hour (±10 min) period. The infusion could be administered any time during the subject's course of treatment with the other IV antibacterial drug, with the exception that no doses of ceftazidime were permitted within 12 hours of AVYCAZ infusion. The AVYCAZ infusion was timed so as to not interfere with the dosing of the other antibacterial drug. Study visits occurred at screening; Study Day 1 (Baseline/IV Infusion); Study Day 2 (24-

hour assessment); Study Day 3 (48-hour assessment), and a Late Follow-up (LFU) assessment 28-35 days after the infusion.

In Part B, subjects received AVYCAZ over a 2-hour (± 10 min) period every 8 hours (±1 hour). Adjunctive IV antibacterial treatment for suspected co-infection with gram-positive or anaerobic organisms was permitted. Adjunctive coverage for aerobic gram-negative organisms was discouraged but additional gram-negative coverage with the aminoglycosides gentamicin or amikacin could be added per standard of care while awaiting baseline culture and susceptibility results. Study visits occurred at screening; Study Day 1 (Baseline/IV Infusion); daily while receiving treatment (Days 2 to 14); at the End of IV (EOIV) Treatment (within 24 hours after the last AVYCAZ IV infusion); Test of Cure (TOC) (7-14 days after last drug dose); and LFU (28-35 days after last AVYCAZ infusion). Subjects in Part B were allowed to switch to alternative oral therapy or outpatient parenteral antimicrobial therapy **(**OPAT) treatment with another IV antibacterial drug following at least 48 hours of AVYCAZ therapy, as per the Investigator's discretion. If subjects were switched to oral therapy or OPAT, the End of IV Treatment (EOIV) visit would be conducted within 24 hours of AVYCAZ discontinuation. An End-of-treatment (EOT) assessment was conducted within 48 hours after the last oral or OPAT treatment (if applicable). The Test-of-Cure (TOC) assessment was 7-14 days after the last dose of any drug (IV or oral) and Late Follow-Up (LFU) assessment 28-35 days after the last infusion of AVYCAZ.

Emergent infection was defined as a "superinfection" or "new infection". A "Superinfection" was defined as a culture-identified pathogen other than a baseline pathogen during the course of active treatment with study therapy, requiring alternative antimicrobial therapy. A "new infection" was defined as a culture-identified pathogen other than a baseline pathogen at any time after study treatment has finished requiring alternative antimicrobial therapy. A predefined list identified the gram-negative microorganisms considered to be a "pathogen" for the study.

Figure 3. Study C3591024 Outline



Abbreviations: CAZ-AVI = ceftazidime-avibactam; EOIV = End of IV; EOT = End of Treatment; F/U = Follow-Up; hr(s) = hour(s); ICD = Informed Consent Document; IV = Intravenous; LFU = Late Follow-Up; OPAT = outpatient parenteral antimicrobial therapy; TOC = Test of Cure.
Source: Applicant Final Protocol for Study C3591024, Figure 1.

Statistical Analysis Plan

The study was not powered for inferential statistical analyses. In Parts A and B the analysis of safety data was performed using the Safety Analysis Set that consists of all subjects who received any amount of IV study dose AVYCAZ. Descriptive statistics of observed results and the

change from baseline to selected post-baseline time points were presented for clinical laboratory results and vital signs.

Efficacy was not an outcome measure for the single-dose Part A study subjects. In the efficacy analysis for the secondary endpoint of Part B, the Intent-to-Treat (ITT) analysis set was defined as all subjects who have been enrolled, regardless of whether or not treatment was received. All-cause mortality was summarized with counts and proportions of deaths for the ITT analysis set. A descriptive assessment of clinical outcome was made by the Investigator at the EOIV, EOT, TOC, and LFU timepoints. Possible outcomes were clinical cure, clinical improvement (oral/OPAT switch subjects only), clinical failure, or indeterminate. A favorable clinical outcome in the efficacy analyses was defined as clinical cure or clinical improvement.

Clinical outcomes were summarized for the ITT, Modified Intent-To-Treat (MITT) and the micro–ITT Analysis Sets from Part B. The MITT Analysis Set included all subjects who received any amount of AVYCAZ and met minimal predefined disease criteria for study inclusion of at least 1 clinical criterion and at least 1 laboratory criterion or 2 clinical criteria in the presence of, or as a result of, suspected or proven bacterial infection requiring IV antibacterial therapy. Subjects with confirmed infection with a pathogen known to be resistant to AVYCAZ and subjects with a confirmed gram-positive, fungal, parasitic, or viral pathogen as the sole cause of infection were excluded from the MITT Analysis Set. The micro-ITT Analysis Set summarized microbiological responses for subjects who had at least 1 gram-negative pathogen in an adequate initial pre-study culture.

Protocol Amendments

There were two protocol amendments. On June 27, 2019, the enrollment sequence for Part B Cohort 3 (pre-term neonates from birth to ≤ 28 days) was revised to ensure that enrollment of subjects in the multiple dose Part B Cohort 3, the most vulnerable population based on their age, was initiated only after data from the first 4 subjects in the single-dose Cohort 3 of Part A were evaluated. On March 16, 2022, a protocol amendment clarified that corrected age applied only to the enrollment of pre-term infants in Cohort 1 (study subjects > 28 days of age) and not Cohort 3 (study subjects ≤ 28 days of age).

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant states in Study C3591024's clinical study report: "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

The Applicant submitted the required Financial Disclosure information. There were no significant financial conflicts of interested identified among the study site investigators. See Section 15.2 for further information.

Patient Disposition

Table 13 displays patient disposition in the study. 52 subjects were screened for enrollment and 48 subjects were enrolled: 27 subjects in Part A and 21 subjects in Part B. In Part A, 2 enrolled subjects discontinued the study prior to receiving study intervention: 1 subject due to withdrawal by parent/guardian and 1 subject due to the parents' wish to discontinue a venous catheter that was not working. Two of 25 treated subjects, in Part A Cohort 3, were lost to follow-up.

In Part B, 3 subjects discontinued study intervention: 1 subject (Part B, Cohort 2) was discontinued from the study intervention after receiving one AVYCAZ dose due to sudden onset hypertransaminasemia which was attributed to a previous surgical procedure (blood sampling indicated hypertransaminasemia was present prior to administration of the first dose of AVYCAZ). The investigator decided to continue treatment with AVYCAZ at the protocol-specified dose, but with the subject excluded from any PK assessments or analysis of efficacy. Two subjects (in Part B, Cohort 3) discontinued AVYCAZ due to adverse events (AEs). One subject completed the LFU visit, and the other subject died prior to the LFU visit.

All enrolled subjects were included in the ITT population (N=48) (see Table 13). All subjects who received at least one dose of AVYCAZ (N=46) were included in the Safety Analysis Set. In the single-dose Part A, there were 9 subjects enrolled into Cohort 1 (infants > 28 days to < 3 months); 8 subjects in Cohort 2 (term neonates from birth to 28 days); and 8 subjects in Cohort 3 (pre-term neonates from birth to 28 days). In the multiple-dose Part B, there were 8 subjects enrolled into Cohort 1; 5 subjects in Cohort 2; and 8 subjects in Cohort 3.

One subject in Part B, Cohort 2 did not have a plasma PK measurement and was excluded from the PK analysis set (N=45). 16 subjects (76.2%) from Part B were included in the MITT; 5 subjects from the ITT population were excluded from the MITT population because they had a confirmed gram-positive organism as the sole cause of infection. Eleven subjects in Part B were excluded from the Micro-ITT Analysis Set because they did not have a gram-negative pathogen at Screening (1 subject in Cohort 1, all 5 subjects in Cohort 2, and 5 subjects in Cohort 3). The Micro-ITT analysis set included the remaining 10 (47.6%) subjects enrolled in Part B.

Table 13. Subject Disposition Study C3591024

Subject Disposition	Part A (N=27) n (%)	Part B (N=21) n (%)	Part A + Part B N 48) n (%)
Intent-to-Treat (ITT)	27 100.0)	21 100.0)	48 100.0)
Treated	25 92.6)	21 100.0)	46 95.8)
Not Treated	2 7.4)	0	2 (4.2)
Safety Analysis Set (SAS)	25 92.6)	21 100.0)	46 95.8)

Subject Disposition	Part A (N=27) n (%)	Part B (N=21) n (%)	Part A + Part B N 48) n (%)
Pharmacokinetic Analysis Set (PK)	25 92.6)	20 95.2)	45 93.8)
Modified Intent-to-Treat (MITT)	N/A	16 76.2	16 33.3)
Microbiological Intent-to-Treat (Micro-ITT)	N/A	10 47.6	10 20.8)

Source: Applicant's Study C3491024-Report Body Table 6.

The most frequently reported primary infections were sepsis (19 subjects [39.6%]) and UTI (7 subjects [14.6%)] in the ITT population as in Table 14. Other infectious diagnoses reported in more than one subject were: gram-negative rod infection (3 subjects [6.3%]), necrotizing enterocolitis (3 subjects [6.3%]), and gram-positive bacterial infection (2 subjects [4.2%]).

Table 14. Primary Infections Diagnosed in More Than One Subject in Study C3591024

Lowest Level Term	Part A N=27 n (%)	Part B N=21 n (%)	Part A + B N=46 n (%)
Sepsis	7 25.9)	12 (57.1	19 39.6)
Urinary tract infection	4 (14.8)	3 14.3)	7 14.6)
Gram-negative infection	1 (3.7	2 (9.5	3 (6.3)
Necrotizing enterocolitis	3 11.1)	0 (0)	3 (6.3)
Gram-positive infection	2 (7.4	0 (0)	2 (4.2)

Source: Table generated by reviewer, JMP Clinical 17.2.

Protocol Violations/Deviations

Table 15 shows the important protocol violations in Study C3591024. The most frequently reported important protocol deviations occurred within the Procedures/Tests, Laboratory, and Informed Consent categories. In the Procedures/Test category, most deviations were due to procedure/test not performed per protocol. In the Laboratory category, most deviations were due to laboratory test not being done. In the Informed Consent category, most deviations were due to subject's legally authorized representative not signing the informed consent document but giving verbal consent. In the Investigational Product category, 8 subjects (16.7%) had dosing/administration errors and 2 subjects (4.2%) had dispensing errors.

Table 15. Summary of Important Protocol Deviations-ITT Analysis Set

Protocol Deviation Category	Part A (N=27) n (%)	Part B (N=21) n (%)	Part A+B (N=48 n (%)
Number of subjects with at least 1 important protocol deviation	15 55.6)	16 (76.2)	31 (64.6)
Procedures/Tests	7 25.9)	14 66.7)	21 43.8)
Laboratory	7 25.9)	10 47.6)	17 35.4)
Informed consent	3 11.1)	5 23.8)	8 16.7)
Investigational product	6 (22.2)	4 19.0)	10 20.8)
Dosing/Administration error	5 18.5)	3 14.3)	8 16.7)

Source: From Applicant Study C3591024 Clinical Study Report Table 5, modified by clinical reviewer.

Table of Demographic Characteristics

Table 16 shows the demographic and baseline characteristics for subjects included in the Safety Analysis Set. The majority of subjects were enrolled in Europe 35/46 (76.1%) with 7/46 (15.2%) enrolled in the United States.

In Part A over half of the subjects were female (60.0%) and were not Hispanic or Latino (84.0%) and White (72.0%). 40.0% (10/25) of subjects were enrolled in Greece and 20.0% (5/25) in the United States. The median (min, max) age was 25.0 (2, 89) days. The majority of subjects (15/25 [60.0%]) were ≥ 37 weeks gestational age.

In Part B 52.4% (11/21) of subjects were male. One subject's race and two subject's ethnicities were not reported. Of the reported races and ethnicities, all were not Hispanic or Latino (100.0%) and the majority were White (85.7%). 52.4% (11/21) of subjects were enrolled in Italy; 7/21 (33.3%) in Greece; and 2/21 (9.5%) in the United States. The median (min, max) age was 23.0 (6, 86) days. The majority of subjects (13/21 [61.9%]) were ≥ 37 weeks gestational age.

The study enrolled both full term and pre-term infants across the 3 age cohorts:

- Cohort 1 included full term infants or pre-term infants with corrected age > 28 days.
  - Two subjects in Part A, Cohort 1 were born at 34 to 36 weeks gestational age.
  - All subjects enrolled into Part B, Cohort 1 were born at full-term (≥ 37 weeks gestational age).
- In Cohort 2, all subjects enrolled were full-term, as per the inclusion criteria.
- In Cohort 3, all subjects enrolled were pre-term, as per the inclusion criteria. Although eligibility criteria allowed enrollment of pre-term neonates born as early as 26 weeks gestational age, the earliest gestational age of enrolled subjects was 31 weeks.
  - There were 7/9 (77.8%) subjects in Part A and 1/8 (12.5%) subject in Part B who were born at 31 weeks gestational age.
  - The majority of subjects enrolled into Cohort 3 were born at 30 to 33 weeks gestational age (7 subjects [87.5%] in Part A and 5/8 (62.5%) subject in Part B.

The majority of the study subjects (26 subjects [56.5%]) were not breastfed.

Medical Officer (MO) comment: *Although study inclusion criteria were for pre-term neonates as early as 26 weeks gestational age, the earliest gestational age of enrolled subjects in Study C3591024 was 31 weeks. As discussed in Section 6.2, models predicted mean ceftazidime AUC values in pre-term neonates ≥ 26 to 30 weeks gestational age to be higher than in the adult population and to exceed the established threshold for safety of ceftazidime. Given the lack of safety data at the exposure levels predicted in the ≥ 26 to 30 weeks gestational age, we agree with the clinical pharmacology team's recommendation to limit the proposed dosage regimen to pre-term neonates with gestational age ≥ 31 weeks.*

Table 16. Demographic Characteristics of the Safety Analysis Set

Demographic Parameters	Part A (N=25)	Part B (N=21)	Part A + Part B (N=46)
Sex, n (%)			
Male	10 40.0)	11 52.4)	21 45.7)
Female	15 60.0)	10 47.6)	25 54.3)
Age (Days)			
Mean (SD)	32.1 (23. 46)	30.0 (21.08)	31.1 22.19
Median (Min, Max)	25.0 2, 89)	23.0 6, 86)	23.5 (2, 89)
(Q1, Q3)	(19, 48)	(14, 42)	(15, 42)
Race			
White	18 (72.0)	18 85.7)	36 78.3)
Black or African American	2 8.0)	2 9.5)	4 8.7)
Asian	4 16.0)	1 4.8)	5 10.9)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not reported	1 4.0)	0	1 2.2)
Ethnicity			
Hispanic or Latino	2 8.0)	0	2 (4.3)
Not Hispanic or Latino	21 84.0)	21 100.0)	42 91.3)
Not reported	2 8.0)	0	2 (4.3)
Region (optional)			
United States	5	2	7
Rest of the World	20	19	39
Europe	17	18	35
Asia	3	1	4
Country			
Greece	10 40.0)	7 33.3)	17 37.0)
Italy	0	11 52.4)	11 23.9)
USA	5 20.0)	2 9.5)	7 15.2)
Taiwan	3 12.0)	1 4.8)	4 8.7)
Hungary	3 12.0)	0	3 6.5)
Estonia	2 8.0)	0	2 (4.3)
Slovakia	2 8.0)	0	2 (4.3)
Gestational Age			
26-29 weeks	0	0	0
30-33 weeks	7 28.0)	5 23.8)	12 26.1)
34-36 weeks	3 12.0)	3 14.3)	6 13.0)
> 37 weeks	15 60.0)	13 61.9)	28 60.9)
Breastfeeding	9 36.0)	11 52.4)	20 43.5)

Source: Table generated by reviewer, OCS Analysis Studio v1 8.0.

Other Baseline Characteristics

Table 17 shows the most frequently reported baseline medical comorbidities. The most common frequently reported terms were "anemias nonhemolytic and marrow depression" in 15/46 (32.6%) of subjects and hepatic and hepatobiliary disorders 12/46 (26.1%).

Table 17. Baseline Medical Comorbidities: Frequently Reported Highest Level Terms Study C3591024

High Level Term	Subjects n (%)
Anemias nonhemolytic and marrow depression	15 (32.6)
Hepatic and hepatobiliary disorder	12 26.1)
Respiratory disorders NEC	10 21.7)
Cardiac and vascular disorders congenital	8 17.4)
Appetite and general nutritional disorders	6 13.0)
Gastrointestinal inflammatory conditions	5 10.9)

Source: Table generated by reviewer, JMP Clinical 17.2.
Abbreviations: NEC=not elsewhere classified

MO comment: *Safety assessment in this study population of hospitalized infants and neonates < 3 months requiring IV antibacterial therapy is challenging due to the lack of a control group and the baseline medical complexity and acuity of the subjects' health conditions.*

In Part B, in the Micro-ITT Analysis Set (see Table 2), the most frequently reported pathogen was *Escherichia coli* (6/10 [60.0%]). Two subjects in Part B (Cohorts 1 and 3) had isolates that were resistant to ceftazidime (*Escherichia coli* and *Klebsiella pneumoniae*). There were no isolates that were reported as being resistant to AVYCAZ.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects in Part A received a single infusion of AVYCAZ. The median treatment duration of AVYCAZ in Part B was 7.0 days (see Table 18). Subjects in Part B were eligible for a switch to oral therapy or OPAT after at least 48 hours of IV AVYCAZ. Four of 21 (19.0%) subjects in Part B were transitioned from AVYCAZ to oral antibacterial drugs (amoxicillin, cefixime, trimethoprim/sulfamethoxazole) as allowed per protocol. All four subjects that transitioned to oral antibacterial therapy were from Cohort 1. No subjects in Cohorts 2 or 3 transitioned to oral antibacterial therapy. No study subject transitioned to OPAT.

Table 18. Mean and Median Treatment Duration Part B Study C3591024

Duration of Treatment* (Days)	Cohort 1 N=8	Cohort 2 (N=5)	Cohort 3 N=8
Mean (SD)	6.38 3.249)	5.00 3.536)	6.50 3.586
Median (Min, Max)	7.00 3.0, 12.0)	4.00 1.0, 10.0)	6.5 2.0, 12.0)
(Q1, Q3)	(3.0, 8.0	(3.0, 7.0	(3.5, 9.0
1	0	1 20.0%	0
2	0	0	1 12.5%
3	3 37.5%	1 20.0%	1 12.5%
4	0	1 20.0%	1 12.5%
5	0	0	0
6	0	0	1 12.5%
7	3 37.5%	1 20.0%	2 25.0%

Duration of Treatment* (Days)	Cohort 1 (N=8	Cohort 2 (N=5)	Cohort 3 N=8
8	0	0	0
9	1 12.5%	0	0
10	0	1 20.0%	0
11	0	0	1 12.5%
12	1 12.5%	0	1 12.5%
13	0	0	0

Source: Applicant Table 14.4.1.1.
* Duration of treatment is the number of calendar days from the first infusion to last infusion.

In Part A, 24/25 (96.0%) of subjects received prior antibacterial medications and 23/25 (92.0%) subjects received concomitant antibacterial medications. One subject (subject (b) (6); Part A Cohort 2) did not have antibacterial medications reported in the case report form but was assessed by the investigator as having met inclusion criteria for being hospitalized and receiving IV antibacterial therapy. The most frequently reported concomitant antibacterials were amikacin (6 subjects [24.0%]) and meropenem or vancomycin (4 subjects [16.0%]), each.

In Part B, 17/21 (81.0%) subjects received prior antibacterial medications and 13/21 (61.9%) subjects received concomitant antibacterial medications. Permissible concomitant antimicrobials included gram-positive coverage (linezolid or vancomycin), aminoglycosides (amikacin or gentamicin) for suspected multidrug resistance, metronidazole for anaerobic coverage, or amphotericin B for antifungal coverage. The most frequently reported concomitant antibacterial medications were vancomycin 9/21 (42.6%); amikacin 6/21 (28.6%); or metronidazole 2/21 (9.5%). Additional concomitant medications received each by 1 subject were amphotericin B and gentamicin. Additionally, two subjects received nonpermitted concomitant antibacterial drugs during the study including cefazolin, meropenem, and off-study AVYCAZ (see narrative for Participant (b) (6) in Dropouts and/or Discontinuations Due to Adverse Effects subsection). Concomitant antibacterial medications were not restricted following EOIV and the majority (17/21 [81.0%]) of Part B subjects received treatment with other antibacterials during follow-up for infection-related AEs including sepsis, suspected sepsis, or necrotizing enterocolitis.

Efficacy Results – Secondary and Other Relevant Endpoints

The primary endpoints of Study C3591024 were PK, safety, and tolerability. Efficacy endpoints were evaluated as a secondary objective in Part B of the study including all-cause mortality, clinical outcome at EOIV, EOT, TOC, and LFU, cure defined as clinical improvement and no need for further antibacterial treatment 7 to 14 days after end of treatment, microbiological eradication 7 to 14 days after end of treatment (micro-Intent-to-Treat analysis set), and emergent infections.

All-Cause Mortality

One subject in Cohort 3 (pre-term neonates) died on Study Day 35. All-cause mortality was 1/21 (4.8%) at the LFU timepoint 28-35 days after the last IV infusion of AVYCAZ. In addition, a second subject in Cohort 1 (a full-term neonate) died on Study Day 67, after completing the LFU Visit. The latter death occurred outside of the active data collection period for the study and

therefore is not included in the analysis of all-cause mortality. Both subjects' deaths are reviewed in Section 8.2.4. Neither death was considered related to study intervention.

Clinical Outcome

Favorable clinical outcome (defined as clinical cure or clinical improvement) rates of >80% were seen at EOIV, EOT, LFU, and TOC as shown in Table 19.

Microbiological Eradication

Eleven subjects in Part B were excluded from the Micro-ITT Analysis Set because they did not have a gram-negative pathogen isolated at screening. Of the 10 subjects included in the Micro-ITT Analysis Set, 80% (8/10) had a favorable microbiological response (eradication or presumed eradication) at TOC. Six of the 8 subjects with a favorable microbiological response had *E.coli* isolates, one had *Klebsiella oxytoca* and one had *Klebsiella pneumoniae*. One subject, with *Citrobacter koseri* as the primary pathogen, had missing data for microbiological response. An unfavorable microbiological response was reported for one subject, with *E. cloacae* complex as the primary pathogen because the subject was assessed as a clinical failure at EOIV due to presumed persistent infection. The *E. cloacae* complex baseline pathogen was not, however, culture-verified to be persistent.

Emergent Infections

No emergent infections were identified.

Table 19. Clinical Outcome (Part B) – ITT Analysis Set

Visit Outcome	Cohort 1 n (%)	Cohort 2 n (%)	Cohort 3 n (%)	All
End of IV treatment	8	5	8	21
Favorable outcome	8 100.0)	4 80.0)	6 75.0)	18 85.7)
Cure	2 25.0)	2 (40.0)	3 37.5)	7 33.3)
Improvement	6 75.0)	2 (40.0)	3 37.5)	11 52.4)
Indeterminate	0 (0)	1 20.0)	1 12.5)	2 9.5)
Failure	0 (0)	0 (0)	1 12.5)	1 4.8)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
End of Treatment	8	5	8	21
Favorable outcome	8 100.0)	4 80.0)	6 75.0)	18 85.7)
Cure	6 75.0)	3 (60.0)	3 37.5)	12 57.1)
Improvement	2 25.0)	1 20.0)	3 37.5)	6 28.6)
Indeterminate	0 (0)	1 20.0)	0 (0)	1 4.8)
Failure	0 (0)	0 (0)	1 12.5)	1 4.8)
Missing	0 (0)	0 (0)	1 12.5)	1 4.8)
Test of Cure	8	5	8	21
Favorable outcome	7 100)	3 (60.0)	7 87.5)	17 85.0)
Cure	7 100)	3 (60.0)	7 87.5)	17 85.0)
Indeterminate	0 (0)	2 (40.0)	0 (0)	2 10.0)
Failure	0 (0)	0 (0)	1 12.5)	1 5.0)
Missing	1 (5.0)[a]	0 (0)	0 (0)	1 (5.0)

Visit Outcome	Cohort 1 n (%)	Cohort 2 n (%)	Cohort 3 n (%)	All
Late Follow-up	8	5	8	21
Favorable outcome	8 100)	4 80.0)	6 75.0)	18 85.7)
Cure	8 100)	4 80.0)	6 75.0)	18 85.7)
Indeterminate	0 (0)	1 20.0)	0 (0)	1 4.8)
Failure	0 (0)	0 (0)	1 12.5)	1 4.8)
Missing	0 (0)	0 (0)	1 12.5)	1 4.8)

Source: Table generated by reviewer, JMP Clinical 17.2
[a.] Subject (b) (6) did not have TOC outcome data due to a missed visit; outcome updated to "missing" in reviewer analysis.

MO comment: *Study C3591024 was a single-arm study without a control group and efficacy was a secondary endpoint for the multi-dose Part B. A positive clinical outcome was defined as clinical cure or clinical improvement. It is encouraging that a favorable response was seen in > 80% of subjects at EOIV, EOT, LFU, or TOC, similar to the prior adult trials with AVYCAZ for the treatment of cIAI, cUTI, or HABP/VABP.*

However, due to substantial heterogeneity with the underlying infection, with the most common infection listed as "Sepsis," the interpretation of the clinical outcome data is limited. There were few participants in Study C3591024 enrolled specifically for the treatment of cIAI, cUTI including pyelonephritis, or HABP/VABP. Three subjects in Part A had a primary infection diagnosis of necrotizing enterocolitis, the most common cause of cIAI in the first month of life. But given these subjects were in the single-dose Part A, efficacy was not an outcome evaluated. No subjects in Part B had necrotizing enterocolitis as a primary diagnosis. UTI was the second most frequently reported infection and was a primary diagnosis in 3 subjects in Part B. No subjects had pneumonia as a primary diagnosis.

8.1.3. Integrated Assessment of Effectiveness

The reviewer notes that due to the high association of anatomic abnormalities with UTIs in the neonate and infant population, all UTIs in this population are considered cUTI. Additionally, the most common etiology of cIAI in the first month of life is necrotizing enterocolitis or spontaneous intestinal perforation as opposed to ruptured appendicitis among infants and older children or adults. However, the mechanism of action of AVYCAZ and the disease pathophysiology and clinical manifestations are sufficiently similar to support extrapolation of effectiveness from adults to the neonate and infant population for the indications of cIAI, cUTI, and HABP/VABP. Therefore, with the PK data from Study C3591024 for infants and neonates from birth (gestational age ≥ 31 weeks) to < 3 months confirming that AVYCAZ exposures associated with efficacy in adult trials are achieved with the proposed dosing regimens, efficacy of AVYCAZ for the treatment of cIAI, cUTI, and HABP/VABP in pediatric patients < 3 months of age can be extrapolated from adults.

8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review is based on the evaluation of data from a phase 2a, two-part, open-label, non-randomized, multicenter, single and multiple dose study to evaluate PK, safety, and tolerability of AVYCAZ in pediatric patients < 3 months of age with suspected or confirmed infections due to gram-negative pathogens requiring intravenous antibacterial treatment (Study C3591024) see Table 11. Safety assessments occurred through the late follow-up (LFU) visit between study days 28 and 35. Safety data from the 46 pediatric subjects < 3 months of age in this study who received at least one dose of AVYCAZ are reviewed below and considered in the context of the safety findings from prior clinical studies evaluating AVYCAZ treatment in older pediatric and adult subjects (see Table 48). These prior studies will be discussed further in Section 8.2.8.

8.2.2. Review of the Safety Database (Study C3591024)

Overall Exposure and Patient Demographics

Study C3591024 was a 2-part study in hospitalized neonates and infants from birth to <3 months of age. Part A subjects received a single-dose of AVYCAZ with a primary objective to characterize PK. Subjects eligible for Part A were hospitalized neonates and infants with bacterial infection receiving IV antibacterial therapy. Part B subjects received two to 14 days of IV treatment with AVYCAZ (with an optional oral or outpatient parenteral antimicrobial therapy switch after 48 hours) with a primary objective to evaluate the safety and tolerability of AVYCAZ. Subjects eligible for Part B were hospitalized neonates and infants with suspected or confirmed aerobic gram-negative bacterial infection requiring intravenous antibacterial therapy, excluding those with suspected or confirmed central nervous system (CNS) infection. The safety analysis set (SAS) consists of all subjects who received any amount of AVYCAZ.

Adequacy of the Safety Database

While the safety database was small, it was considered acceptable in terms of the number of subjects in each predefined age group given the known safety profile of ceftazidime-avibactam and difficulties in recruiting hospitalized infants and neonates < 3 months of age requiring IV antibacterial therapy. Safety evaluations included vital signs, routine physical examinations, and laboratory tests. Subjects were monitored for AEs including cephalosporin class effects.

MO comment: *This is a small study with a limited sample size. The majority of subjects were non-Hispanic and White with only 4 Black or African American subjects enrolled. Only 21 subjects were enrolled in Part B, the multiple dose component, of the study. Subjects in Part B received a median treatment duration of 7 days with the longest duration being 12 days. The recommended AVYCAZ duration of treatment for cIAI is 5 to 14 days: cUTI including pyelonephritis and pyelonephritis 7 to 14 days (Allergan, 2022). Only 5 subjects received > 7*

days of AVYCAZ. There is limited information on the safety of prolonged treatment courses with AVYCAZ in neonates and infants < 3 months.

8.2.3. 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 this study. The data were submitted in standardized formats for review.

Categorization of Adverse Events

Accurate definitions of AEs and serious adverse events (SAEs) were provided in the protocol. AEs were summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, version 25.1), by relationship to study therapy, and by severity.

Severity of AEs was assessed as mild, moderate, or severe as follows:

- Mild: Does not interfere with subject's usual function
- Moderate: Interferes to some extent with subject's usual function
- Severe: Interferes significantly with subject's usual function

An SAE was defined as any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/birth defect
- Is considered to be an important medical event in the opinion of the investigator

The time period for collection of AEs for each subject ranged from the time the subject provided informed consent through a minimum of 28 calendar days after the last administration of the investigational product. All serious and nonserious AEs were recorded in the case report form (CRF) and SAEs were reported to the Applicant within 24 h of onset.

Causality assessments were performed by the investigator for all AEs (serious and non-serious). An investigator's causality assessment is defined as the investigator's determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE.

Routine Clinical Tests

Routine clinical laboratory tests performed at screening and end of IV (EOIV) visits included complete blood count (CBC) with differential, chemistry panel, and urinalysis. Additional samples may be collected during the treatment period if clinically indicated. At screening and throughout the treatment period (until the TOC visit), the results of Chest X-ray, CT scan, or other imaging tests (e.g., echocardiogram, CT scan, MRI, ultrasound) as well as laboratory assessments of C-reactive protein (CRP) or procalcitonin were obtained if performed as part of the subject's regular medical care.

Brief physical examinations including, but not limited to weight and physical findings related to bacterial infection or sepsis; presence of central venous catheter; presence of other medical devices such as ventilator, cardiac devices, cerebrospinal fluid (CSF) shunts, orthopedic transplants, or urinary catheter was done at screening and at subsequent visits. Length was recorded at screening. At least two sets of vital signs including heart rate/pulse, blood pressure, respiratory rate, temperature, and oxygen saturated were recorded over a 30-minute period at each visit.

For Part A, study visits occurred at screening; Study Day 1 (Baseline/IV Infusion); Study Day 2 (24-hour assessment); and Study Day 3 (48-hour assessment), and a Late Follow-up (LFU) assessment 28-35 days after the infusion. In Part B, study visits occurred at screening; Study Day 1 (Baseline/IV Infusion); daily while receiving treatment (Days 2 to 14); at the End of IV Treatment (≤ 24 hours after last IV infusion); End of Treatment (≤ 48 hours after last drug dose); Test of Cure (7-14 days after last drug dose); and Late Follow-Up (28-35 days after last AVYCAZ infusion).

MO comment: *Types and frequencies of clinical assessments were acceptable.*

8.2.4. Safety Results

Overview of Adverse Events

Table 20 displays an overview of treatment emergent adverse events (TEAEs) from Study C3591024. Study investigators identified one TEAE considered related to the study intervention, oxygen saturation decreased, which was assessed as a mild TEAE. A total of 24 subjects had a TEAE (8/25 [32.0%] in Part A; 16/21 [76.2%] in Part B) with a total of 71 TEAEs reported (26 in Part A; 45 in Part B), 5 subjects had TEAE of severe intensity (1 in Part A; 4 in Part B). There were 8 subjects with SAEs (3 in Part A; 5 in Part B) and 2 subjects had SAEs leading to discontinuation of study intervention in Part B.

Table 20. Overview of Subjects With Treatment-Emergent Adverse Events Through LFU (Study C3591024)

Adverse Event Category	Part A N = 25 n (%)	Part B N = 21 n (%)	Part A + Part B N=46 n (%)
Any TEAE	8 (32.0)	16 (76.2)	24 52.2)
TEAE related to study intervention	1 (4.0)	0	1 (2.2)
Any TEAE with outcome leading to death	0	1 (4.8	1 2.2)
Any SAE	3 12.0)	5 23.8)	8 17.4)
Any TEAE leading to discontinuation of study treatment	0	2 9.5)	2 (4.3)
Any TAE with severe intensity	1 4.0)	4 19.0)	5 10.9)

Source: Table generated by reviewer, OCS Analysis Studio v1 8.0.

Deaths

No deaths were reported in Part A. Two deaths were reported in Part B: 1 during the study (Study Day 35) and 1 after study completion (Study Day 67; 55 days after the end of study treatment). Both deaths were assessed as unrelated to study intervention by the investigator and attributed to severe underlying conditions.

MO comment: *As reviewed in detail in the following narratives, I agree with the study investigators that neither event of death was related to AVYCAZ and both deaths can be attributed to the severe underlying medical comorbidities.*

The following case narratives describe the events in greater detail:

- Subject (b) (6) (SAE: Renal failure; Electrocardiogram QT prolonged; Necrotizing colitis; Septic shock): A 5-week-old female with a medical history of multiple congenital abnormalities, hypertrophic cardiomyopathy, hypertransaminasemia, and cholestatic jaundice was enrolled in Part B with the primary diagnosis of "sepsis." At baseline, the subject had normal renal function. The day prior to study initiation, the subject was started on antibacterial therapy with ampicillin, gentamicin, and metronidazole. On study enrollment, ampicillin was discontinued, and gentamicin and metronidazole were continued in addition to AVYCAZ. On Study Day 7, the subject was diagnosed with renal failure (creatinine 1.3 mg/dL and blood urea 41 mg/dL) and an electrocardiogram showed clinically significant QT prolongation. Concomitant propranolol may have contributed to lengthening of the QT. A consulting nephrologist recommended discontinuing AVYCAZ (on day 7 of treatment) as well as captopril and gentamicin due to the SAE of "renal failure". On Study Day 15, laboratory tests showed improvement in renal function (creatinine 0.74 mg/dL and blood urea 18 mg/dL). The prolonged QT was reported as resolved on Study Day 24. On Study Day 34, the subject experienced necrotizing enterocolitis (NEC) and septic shock with a lactic acid of 15.9 mmol/L. The subject had rapid worsening of her general clinical condition and died on Study Day 35.

MO comment: *I agree with the investigators assessments as above that the events of death, septic shock, and NEC do not seem related to AVYCAZ given that the events occurred >3 weeks after discontinuation of study intervention. It is plausible that AVYCAZ may have contributed to*

renal dysfunction prior to its discontinuation; however, it is more likely that captopril and gentamicin were the etiologic agents given their known association with nephrotoxicity. I agree with the assessment that QT prolongation could be explained by concomitant administration of propranolol, which is primarily renally excreted, in the setting of an acute kidney injury.

- Subject (b) (6) (SAE: Enterobacter sepsis; Candida sepsis): A 6-week-old female with epidermolysis bullosa was enrolled in Part B with primary diagnosis of sepsis and received 12 days of AVYCAZ. On Study Day 23, the subject experienced sepsis due to *Enterobacter cloacae* bacteremia. On Study Day 33, the subject developed *Candida parapsilosis* fungemia. The subject died on Study Day 67 with worsening of her underlying severe skin condition. The investigator did not consider the Enterobacter or Candida sepsis related to AVYCAZ.

MO comment: *I agree that Enterobacter sepsis; Candida sepsis; and the eventual event of death are unlikely due to AVYCAZ and are more plausibly explained by worsening of the underlying skin condition, epidermolysis bullosa.*

Serious Adverse Events

Eight subjects experienced SAEs (3 in Part A; 5 in Part B) as described in Table 21. The only SAEs reported in > 1 subject were necrotizing colitis and sepsis, which were not unexpected given the patient population enrolled. NEC occurred in one subject in Part A and one in Part B. Sepsis occurred in two subjects in Part B. No subject experienced an SAE that was attributed to AVYCAZ by the investigator.

Table 21. Serious Adverse Events by System Organ Class and Preferred Term (Study C3591024)

System Organ Class Preferred Term	Part A N = 25 n (%)	Part B N = 21 n (%)	Part A + Part B N = 46 n (%)
Any SAE	3 (12.0	5 23.8)	8 17.4)
Blood and lymphatic system disorders	0	1 4.8)	1 2.2)
Neutropenia	0	1 4.8)	1 2.2)
Cardiac disorders	0	1 4.8)	1 2.2)
Cardiac failure acute	0	1 (4.8	1 2.2)
Gastrointestinal disorders	1 (4.0)	1 (4.8	2 (4.3)
Necrotizing colitis	1 (4.0)	1 (4.8	2 (4.3)
Infections and infestations	1 (4.0)	4 19.0)	5 10.9)
Candida sepsis	0	1 (4.8	1 2.2)
COVID-19	1 (4.0)	0	1 2.2)
Enterobacter sepsis	0	1 (4.8	1 2.2)
Enterococcal sepsis	0	1 (4.8	1 2.2)
Sepsis	0	2 (9.5	2 (4.3)
Septic shock	0	1 (4.8	1 2.2)
Investigations	1 (4.0)	1 (4.8	2 (4.3)
Electrocardiogram QT prolonged	0	1 (4.8	1 2.2)
Hepatic enzyme increased	1 (4.0)	0	1 2.2)
Renal and urinary disorders	0	2 (9.5	2 (4.3)
Oliguria	0	1 (4.8	1 2.2)
Renal failure	0	1 (4.8	1 2.2)
Respiratory, thoracic and mediastinal disorders	0	1 (4.8	1 2.2)
Acute respiratory failure	0	1 (4.8	1 2.2)

Source: Table generated by reviewer, OCS Analysis Studio v1 8.0, Safety Explorer.

Two of the subjects with SAEs ([(b) (6)] and [(b) (6)]) who died are discussed above. The following case narratives describe the other 6 subjects with SAEs in greater detail.

Part A

- Subject [(b) (6)] (SAE: Necrotizing colitis): a 5-week-old female with a medical history of NEC, a double inlet left ventricle, congenital musculoskeletal disorder, pulmonary vascular disorder with a history of pulmonary artery banding and hematochezia, and feeding disorder developed bloody stool and was diagnosed with NEC on Study Day 16. The event was serious due to prolonged hospitalization. Given the prior history of NEC, NEC recurrence was assessed as unrelated to AVYCAZ.
- Subject [(b) (6)] (SAE: COVID-19): A 3-week-old female developed COVID-19 on Study Day 14. A close relative was also diagnosed with COVID-19 around the same time.
- Subject [(b) (6)] (SAE: Hepatic enzyme increased): A 7-week-old female with a history of food protein-induced enterocolitis syndrome had elevated liver enzymes (Alanine Aminotransferase (ALT) 107 IU/L [normal range: 13-45 IU/L] and Aspartate Aminotransferase (AST) 59 IU/L [normal range: 12-45 IU/L]) before enrollment into the study. Liver enzymes remained elevated on Study Day 20 with ALT 115 IU/L and AST 132 IU/L. The subject was hospitalized on Study Day 21 to evaluate the liver enzyme elevation which was assessed as possibly related to the subject's food protein-induced enterocolitis syndrome.

Part B

- Subject [(b) (6)] (SAEs: Sepsis; Enterococcal sepsis): A 1-week-old male with gastroschisis and intestinal atresia with history of jejunostomy requiring parenteral nutrition received AVYCAZ per protocol from Study Day 1 until Study Day 10 for treatment of sepsis. Blood cultures on Study Day 1 grew *Staphylococcus epidermidis* for which the subject was also treated with IV vancomycin through Study Day 18. On Study Day 36, the subject developed sepsis from *Enterococcus faecium* bacteremia. The Investigator assessed the event as unrelated to AVYCAZ but rather related to the underlying gastrointestinal disorder or indwelling central venous catheter required for parenteral nutrition.
- Subject [(b) (6)] (SAEs: Sepsis; Cardiac failure acute): A 2-week-old male with prematurity, ventricular septic defect, and cholestasis with a primary infectious diagnosis of sepsis received AVYCAZ per protocol from Study Day 1 until Study Day 12 when the subject was diagnosed with acute cardiac failure due to possible sepsis. On Study Day 12, abnormal labs included elevated lactic acid and procalcitonin with brain natriuretic peptide (BNP) 19.088 pg/mL. Due to suspected sepsis and laboratory abnormalities, on Study Day 12, the investigator discontinued AVYCAZ and transitioned to linezolid and meropenem. The subject was also started on levosimendan and milrinone for treatment of acute cardiac failure. Levosimendan was discontinued on Study Day 15 and the event of acute cardiac failure was assessed as resolved. On Study Day 21, BNP was markedly elevated at 2886 pg/mL. The event of sepsis was reported as resolved on Study Day 26 and CRP had

decreased to 0.03 mg/dL on Study Day 27. The subject continued on milrinone at the end of the study for heart failure. The investigator assessed sepsis and worsening of acute cardiac failure as unrelated to AVYCAZ treatment.

- Subject (b) (6) (SAEs: Acute respiratory failure; Oliguria; Neutropenia): A 2-week-old male received AVYCAZ per protocol from Study Day 1 until Study Day 7 for sepsis. On Study Day 1, the subject was tachypneic and vancomycin was started. On Study Day 2, the subject experienced oliguria and acute respiratory failure with a right pleural effusion requiring intubation with mechanical ventilation. On Study Day 3, oliguria resolved but the subject developed neutropenia with an absolute neutrophil count of 800 cells/mm^3. The neutrophil nadir was 150 cells/mm^3 on Study Day 4. On Study Day 5, neutropenia resolved, and the subject had clinically improved breathing spontaneously in ambient air with a neutrophil count of 3,473 cells/mm^3. The investigator assessed the neutropenia, oliguria, or respiratory failure events as unrelated to AVYCAZ.

MO comment: *I agree with the investigators' assessments that reported SAEs were unlikely to be related to AVYCAZ. Subject (b) (6) had an SAE of increased hepatic enzymes which is a listed adverse reaction of AVYCAZ; however, liver enzymes were elevated prior to receiving AVYCAZ making the hepatic enzyme elevation unlikely to have been caused by AVYCAZ. Subject (b) (6) developed oliguria and neutropenia. While renal impairment and neutropenia are both listed adverse reactions of AVYCAZ, the subject's oliguria and neutropenia resolved under the continuous administration of AVYCAZ. I agree with the investigator and Applicant that oliguria and neutropenia were unlikely to have been caused by AVYCAZ but were likely due to sepsis and acute respiratory failure.*

Dropouts and/or Discontinuations Due to Adverse Effects

One subject in Part B, Cohort 2 (Subject (b) (6) discontinued study treatment after receiving 1 dose of AVYCAZ due to sudden onset hypertranaminasemia which was attributed to a previous surgical procedure (the blood sampling indicating hypertransaminasemia was taken prior to administration of the first dose of AVYCAZ). The investigator decided to transition treatment from study AVYCAZ to commercial AVYCAZ at the protocol-specified dose, but with the subject excluded from any PK assessments or analysis of efficacy. The subject received a total duration of 11 days of AVYCAZ (study drug and commercial).

Two subjects in Part B, Cohort 3 experienced SAEs that led to discontinuation of the study intervention as discussed above. One of these subjects completed follow-up, Subject (b) (6) discontinued study treatment due to suspected sepsis and abnormal labs including elevated lactic acid, procalcitonin, and BNP. The other subject, Subject (b) (6) died before completing follow-up. Subject (b) (6) discontinued study treatment due to acute renal failure and QT prolongation.

Significant Adverse Events

Known cephalosporin class effects including diarrhea, liver disorders, hypersensitivity reactions, hematological disorders, and renal disorders were deemed as AEs of special interest (AESI)**.**

Diarrhea

One subject in Part B ([(b) (6)] had one day of mild diarrhea. No cases of *Clostridioides difficile* diarrhea were reported.

Liver Disorders

The most frequently identified AESI was hepatic enzyme elevations which was reported in 4 subjects (4/46; 8.7%) as 5 TEAEs [reported as events of 2 "hepatic enzyme increased"; 2 elevated "transaminases"; one "Alanine aminotransferase increase"]. These liver disorders were reported in 1 subject in Part A and 3 subjects in Part B. As discussed below, there were no potential Hy's Law cases identified.

Part A (Single Dose)

- Subject [(b) (6)] (Cohort 1): AST and ALT were elevated at baseline. ALT increased on Study Day 2 before decreasing on Study Day 3. In contrast, AST was highest at baseline before decreasing on Study Day 2 and Study Day 3.

Part B (Multiple Dose)

The three subjects from Part B, all in Cohort 1, with elevated liver enzymes had worsening liver enzyme elevation while on AVYCAZ which may have been treatment related. All three of these subjects received 7 days of AVYCAZ.

- Subject [(b) (6)] (Cohort 1): AST and ALT were normal at baseline. Both AST and ALT peaked on day 5 before down-trending on day 7 (End of IV).
- Subject [(b) (6)] (Cohort 1): AST and ALT were normal at baseline. Both AST and ALT were elevated at End of IV (Study Day 7). AST peaked on Study Day 7 while ALT peaked on Study Day 12.
- Subject [(b) (6)] (Cohort 1): AST was elevated at baseline, but ALT was normal at baseline. On Study Day 5 both AST and ALT were elevated. The subject had a reported adverse event of an "Influenza-like illness" on Study Day 6. AVYCAZ was discontinued on Study Day 7. Both AST and ALT peaked on Study Day 11.

MO comment: *Transaminitis will be communicated in the labeling as an adverse reaction occurring in > 3% of infants and newborns < 3 months of age. The AVYCAZ labeling has previously included that AST and ALT elevations occurred at a rate of less than 1% of adults in the AVYCAZ phase 3 trials. Elevated liver enzymes were also seen in the phase 3 clinical trials of FORTAZ and "hepatic dysfunction including cholestasis" is listed as a "Cephalosporin-Class Adverse Reaction" in the FORTAZ label.*

Subject [(b) (6)] (from single-dose Part A) had intermittent elevations in their transaminases which were attributed to "food protein-induced enterocolitis syndrome"; however, ALT increased following AVYCAZ administration making it impossible to rule-out a concurrent drug toxicity. We are additionally unable to rule-out that subjects [(b) (6)] and [(b) (6)] liver

enzyme elevations were not due to AVYCAZ. Subject [redacted] had normal liver enzymes at baseline which became elevated during treatment with AVYCAZ and did not downtrend until after AVYCAZ was discontinued. Subject [redacted] developed worsening of AST elevation and new onset ALT elevation which both down-trended after AVYCAZ was discontinued. Based on the time course of liver enzyme elevations, it seems less likely that Subject [redacted]'s liver enzyme elevation was due to AVYCAZ, due to a marked decline in the liver enzymes while receiving AVYCAZ.

Hematological Disorders

Two subjects had neutropenia ([redacted] and [redacted] Subject [redacted] was discussed in detail above and neutropenia was not assessed by the investigator as related to AVYCAZ since it resolved despite ongoing treatment. Subject [redacted] had an absolute neutrophil count nadir of 1,144 cells/mm^3 at the TOC visit which had decreased from 1,900 cells/mm^3 at the EOIV visit. Neutropenia resolved on the follow-up visit.

"Anemia" or "anemia neonatal" were recorded as TEAEs in 1/25 (4.0%) of subjects in Part A and 3/21 (14.3%) of subjects in Part B. All of the subjects with AEs of anemia were from Cohorts 2 or 3, the two cohorts of subjects less than 28 days of age.

Part A (Single Dose)

- Subject [redacted] (Cohort 3): Worsening "neonatal anemia" that was recorded as starting and ending on Study Day 2.

Part B (Multiple Dose)

- Subject [redacted] (Cohort 3): Worsening anemia during AVYCAZ treatment. Worsening anemia was reported on Study Day 3 and resolved on Study Day 13 (last dose of AVYCAZ on Study Day 6).
- Subjects [redacted] (Cohort 2) and [redacted] (Cohort 3): anemia occurred following the discontinuation of AVYCAZ.
  - Subject [redacted] transitioned from study AVYCAZ to commercial AVYCAZ as described in the Dropouts and/or Discontinuations Due to Adverse Effects subsection above and completed AVYCAZ on Study Day 11. Anemia was reported on Study Day 24 and resolved on Study Day 29.
  - Subject [redacted] had their last dose of AVYCAZ on Study Day 3 and the event of worsening anemia occurred on Study Day 11 which resolved on Study Day 31.

MO comment: *It is challenging to interpret the TEAEs of anemia due to the high background prevalence of anemia prior to study treatment, with "anemia" or "anemia neonatal" reported in 15/46 (32.6%) of subjects as components of the General Medical History and reported as a TEAE in 4/46 (8.7%) during the study period. Subject [redacted] was the only subject with both an anemia event reported in the medical history ("anemia neonatal") as well as an AE of an anemia*

event. There does not appear to be a temporal relationship between AVYCAZ and anemia with only one subject developing anemia while receiving AVYCAZ.

Coombs seroconversion was not assessed as part of this study. Hemolytic anemia was not reported as an adverse event. It is reassuring that there was not overlap between the subjects with elevated liver enzymes or anemia as may have been expected with a Coombs' immune hemolytic anemia.

Hypersensitivity Reactions

One subject ((b) (6) in Part A had a maculopapular rash on screening prior to receiving AVYCAZ. No hypersensitivity reactions were identified during the study.

Renal Disorders

In Part A, one subject ((b) (6) developed oliguria on Study Day 2 which resolved later on the same day and was rated as mild. The investigator did not consider oliguria to be related to AVYCAZ. In Part B, there was 1 case of renal failure ((b) (6) and one of oliguria ((b) (6) both are described above (Subject (b) (6) [described under the Serious Adverse Events subsection] and (b) (6) [described under the Deaths subsection]. There were alternative etiologies to explain renal insufficiency for both subjects in Part B and neither subjects' investigator attributed these renal disorders to AVYCAZ.

Treatment Emergent Adverse Events

Twenty-four subjects had at least one TEAE (8 in Part; 16 in Part B) with a total of 72 TEAEs (26 in Part A; 46 in Part B). 5 subjects had TEAE of severe intensity (1 in Part A; 4 in Part B). The majority of TEAEs were mild or moderate in severity. Table 22 is a summary of TEAEs observed in > 1 study subject in Study C3591024. The most common TEAEs were "sepsis", "transaminases increased", "anemia", "renal disorders", and "vomiting".

Table 22. Summary of TEAEs Observed in > 1 Study Subject in Study C3591024

TEAE	Part A N = 25 n (%)	Part B N = 21 n (%)	Part A + Part B N = 46 n (%)
Sepsis	0	5 23.8)	5 (10.9
Transaminases increased[a]	2 8.0)	3 14.3)	5 10.9)
Anemia[b]	1 4.0)	3 14.3)	4 8.7)
Renal disorders[c]	1 4.0)	2 9.5)	3 6.5)
Vomiting	1 4.0)	2 9.5)	3 6.5)
COVID-19	1 4.0)	1 4.8)	2 (4.3)
Electrocardiogram QT prolonged	1 4.0)	1 4.8)	2 (4.3)
Oxygen saturation decreased	1 4.0)	1 4.8)	2 (4.3)
Neutropenia	0	2 9.5)	2 (4.3)
Necrotizing colitis	1 4.0)	1 4.8)	2 (4.3)
Decubitus ulcer	0	2 9.5)	2 (4.3)
Pyrexia	1 4.0)	1 4.8)	2 (4.3)

Source: Table generated by reviewer, OCS Analysis Studio v1 8.0, Safety Explorer
[a.] Includes "Alanine aminotransferase increased", "Transaminases increased", and "Hepatic enzyme increased"
[b.] Includes "Anemia" and "Anemia neonatal"
[c.] Includes "Oliguria" and "Renal failure".

MO comment: *One "mild" TEAE of oxygen saturation decrease in Part A was attributed to AVYCAZ by the investigator. No other TEAE was clearly attributed to the study drug by the investigator. TEAEs occurring in > 1 subject in Study C3591024 which are listed as adverse reactions in the AVYCAZ labeling include: increased hepatic enzymes; renal impairment; vomiting; anemia; and neutropenia. As reviewed in the case narratives, renal or hematologic adverse events can be alternatively explained as complications of the underlying disease process and medical comorbidities. It is noted that all 3 subjects in Part B with increased hepatic enzymes received 7 days of AVYCAZ. One subject in Part A and one subject in Part B had elevated liver enzymes at baseline. Only 5 subjects in the study received >7 days of AVYCAZ. The median treatment duration in Study C3591024 was 6 days with a maximum of 12 days; as a result, there are limited data regarding the risk of hepatotoxicity with prolonged treatment courses in neonates and infants < 3 months. The proposed labeling will describe the duration of treatment administered in Study C3591024 and report that the most common adverse reactions occurring in >3% of subjects enrolled in the study were vomiting and increased transaminases.*

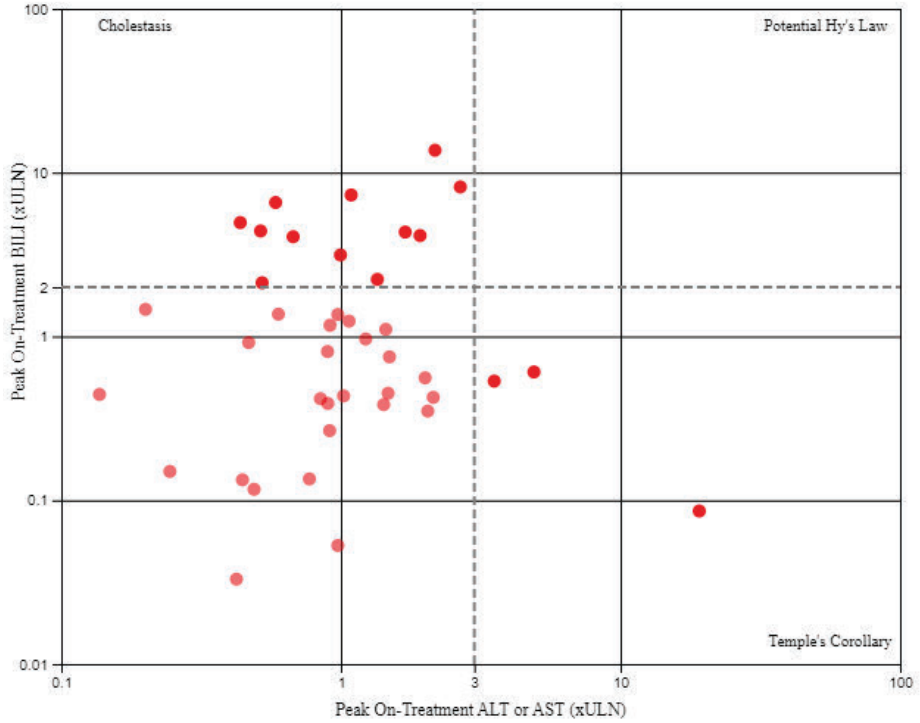
TEAEs of "Sepsis", "COVID-19"; "necrotizing colitis", and decubitus ulcer that were reported in multiple subjects are not surprising given the patient population studied. The TEAE of electrocardiogram QT prolonged was identified in two subjects but in both subjects, the QT prolongation events were attributed by the investigator to concomitant medications.

Laboratory Findings

In Part A, no clinically meaningful mean changes from baseline were observed in hematology, blood chemistry, or urinalysis parameters. One subject had elevated liver enzymes at baseline and ALT increased on Study Day 2 before decreasing on Study Day 3. One subject developed oliguria which resolved later on the same day and was rated as mild. The investigator did not consider these laboratory abnormalities as due to the study intervention.

In Part B, several subjects had increases in lymphocyte counts and lymphocyte/leukocyte ratio which were considered consistent with their underlying conditions. Three subjects had TEAEs of increased liver enzymes, two of the three subjects had normal liver enzyme levels at baseline. All three subjects with increased hepatic enzymes received 7 days of AVYCAZ. No cases met Hy's Law criteria defined as ALT or AST ≥3x ULN, total bilirubin ≥2x ULN, and alkaline phosphatase ≤2 ULN as shown in Figure 4. One subject had a TEAE of renal failure and one subject had a TEAE of oliguria. Three subjects had TEAEs of anemia and two subjects had TEAEs of neutropenia. Neutropenia resolved on follow-up. The investigators did not consider these laboratory abnormalities to be related to the study intervention.

Figure 4. Evaluation of Drug-Induced Serious Hepatotoxicity Plot in Study C3591024



Source: Graph generated by the reviewer, OCS Analysis Studio v1 8.0, Hepatic Explorer.
Filters: None.
Note: Hepatotoxicity Candidates: ALT or AST >= 3*ULN; BILI >= 2*ULN (0-30 days forward); ALP < 2*ULN (0-999 days backward).
Note: Results missing ULN values were imputed using the weighted mean of the lab code.
Abbreviations: ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BILI=bilirubin, DILI=drug-induced liver injury, ULN=upper limit of normal.

Vital Signs

Two subjects had AEs of oxygen saturation decrease. For one subject, in Part A, the mild TEAE of oxygen saturation decrease was assessed as treatment-related by the investigator. There were no other clinically meaningful changes observed in vital sign measurements (systolic blood pressure, diastolic blood pressure, pulse rate, oxygen saturation, respiratory rate, temperature, or weight) in the study.

Physical Examination

In Part A, the majority of subjects had normal physical examination findings at each study visit. In Part B, the majority of subjects had normal physical examination findings at each study visit with the exception of general appearance and skin (e.g., poor general clinical condition, appearance of ill neonate, and jaundiced skin), consistent with and not unexpected in hospitalized neonates and infants (up to 3 months of age) with suspected or confirmed aerobic gram-negative bacterial infections requiring IV antibacterial therapy.

Electrocardiograms (ECGs)/QT

ECGs were not routinely performed as part of the safety assessment for this study. Two subjects had TEAE of QT prolongation (Subjects (b) (6) and (b) (6) Subject (b) (6)'s

event was listed as a SAE as described above. Both QT prolongation events were attributed to concomitant medications. Prior studies showed no clinically significant changes in ECG/QT parameters associated with AVYCAZ exposure.

Immunogenicity

There are no studies evaluating the immunogenicity of ceftazidime or avibactam. Both drugs are small molecules not expected to evoke an immune response.

MO comment: *One subject in Part A had a mild oxygen saturation decrease that the investigator attributed to AVYCAZ. Three subjects had elevated liver enzymes while on treatment with AVYCAZ, which may have been caused by AVYCAZ. No other laboratory, vital sign, or physical examination findings were attributed to AVYCAZ.*

8.2.5. Analysis of Submission-Specific Safety Issues

There were no cases of *C. difficile* associated diarrhea or anaphylaxis in the study. Other cephalosporin class effects are discussed above in the Significant Adverse Events section.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessments were performed for this study.

8.2.7. Safety Analyses by Demographic Subgroups

The evaluation of TEAE or SAE within subgroups of age, sex, or race was limited by small population sizes. There were no obvious differences in the rate or type of AEs seen between the demographic groups. In Part B, the rates of TEAE were highest among the ≤ 28 day old Cohorts 2 and 3 with all 5 (100.0%) of subjects in Part B Cohort 2 (full term neonates) with a TEAE and 7/8 (87.5%) of subjects in Part B Cohort 3 (pre-term neonates) had a TEAE as shown in Table 23. The majority of study participants were White limiting evaluation of AEs stratified by race. There was not a difference in the rate of AEs between male or female sex as shown in Table 24.

MO comment: *A small number of events and small sample sizes preclude reliable conclusions regarding the incidence of TEAE or SAE by demographic subset. The incidence of TEAE was highest among study subjects ≤ 28 days which likely reflects baseline medical comorbidities within this high-risk study population. It is reassuring that SAEs did not appear increased in Part B Cohort 3, the youngest cohort, compared with the other cohorts.*

Table 23. Overall Incidence of TEAE and SAE by Age Cohorts in Study C3591024

	Part A				Part B			
Adverse Event Category	Cohort 1 N=9 n (%)	Cohort 2 N=8 n (%)	Cohort 3 N=8 n (%)	Cohorts 1, 2, 3 N=25 n (%)	Cohort 1 N=8 n (%)	Cohort 2 N=5 n (%)	Cohort 3 N=8 n (%)	Cohorts 1, 2, 3 N=21 n (%)
TEAE	4 (44.4)	2 25.0)	2 25.0)	8 32.0)	4 50.0)	5 100)	7 87.5)	16 76.2)
SAE	2 (22.2)	0 (0)	1 12.5)	3 12.0)	1 12.5)	2 (40.0)	2 25.0)	5 23.8)

Source: Table generated by reviewer, OCS Analysis Studio v1 8.0.

Table 24. Overall Incidence of TEAE and SAE by Sex and Race in Study C3591024

Demographic Category Demographic	Part A N=25 n (%)	Part B N=21 n (%)
Sex		
Female	4/15 26.7)	9/10 90.0)
Male	4/10 40.0)	7/11 63.6)
Race		
White	5/18 27.8)	15/18 83.3)
Black	2/2 100.0)	1/2 (50.0
Asian	1/4 (25.0	0/1 0
Not reported	0/1	N/A

Source: Table generated by reviewer, OCS Analysis Studio v1 8.0.

8.2.8. Specific Safety Studies/Clinical Studies

The study under review for this supplement, C3591024, had safety and tolerability as the primary objective and was the first safety study of AVYCAZ in the neonate and infant pediatric population less than 3 months of age. Safety findings in Study C3591024 were similar to the findings within the AVYCAZ safety database shown in Table 25. The AVYCAZ clinical trial safety database includes subjects enrolled across three additional studies of pediatric patients aged 3 months to <18 years: C3591025 [HABP/VABP], D4280C00015 [cIAI], and D4280C00016 [cUTI]; as well as 6 prior studies in adults, including four phase 3 studies: D4281C00001 (REPROVE) [HABP/VABP], D4280C00006 (REPRISE) [cIAI or cUTI], D4280C00002/4 (RECAPTURE) [cUTI], D4280C00001/5 (RECLAIM 1/2) [cIAI]; and two phase 2 studies: NXL104/2002 [cIAI] and NXL104/2001 [cUTI].

Table 25. Safety in AVYCAZ Clinical Studies Program

Study Category Study	Any TEAE n (%)	Any SAE n (%)	Discontinuation Due to AE n (%)	Deaths n (%)
Phase 2a Infant/Neonate Study				
C3591024 N 46)	23 50.0)	8 17.4)	2 (4.3)	1 (2.2)
Phase 2 Pediatric Studies				
cIAI Study D4280C000015 C3591004 AVYCAZ + MTZ N =61	32 52.5)	5 8.2)	0	0
cUTI Study D4280C000016 C3591005) N 67	36 53.7)	8 11.9)	3 4.5)	0
Phase 1 Pediatric Study				
HABP/VABP Study D4280C00028 C3591024 N 4	3 75.0)	1 25.0)	N/A	0
Phase 3 Adult Studies				
cIAI Study D4280C00001/5 AVYCAZ (+MTZ N 529	243 45.9)	42 7.9)	14 2.6)	14 2.6)
cUTI Study D4280C00002/4 N 511	185 36.2)	21 4.1)	7 1.4)	0
cIAI and cUTI Study D4280C00006 AVYCAZ +MTZ for cIAI N =164	51 31.1)	9 5.5)	1 0.6)	3 1.8)
HABP/VABP Study D4281C00001 N=436)	323 74.1)	79 18.1)	26 (6.0)	16 3.7)
Phase 2 Adult Studies				
cIAI Study NXL104/2002 AVYCAZ +MTZ N=101)	65 64.4)	9 8.9)	6 (6.0)	3 (3.0)
cUTI Study NXL104/2001 N 68	46 67.6)	6 8.8)	2 2.9)	

Source: Generated by the FDA review team.

0

The most common adverse reactions in the prior pediatric studies were diarrhea, vomiting, rash and infusion site phlebitis. The adverse reactions prevalent within the pediatric population are similar to those observed in the adult population. *C.difficile* associated diarrhea has been reported. A summary of safety data from the clinical program is included below:

Complicated Intra-Abdominal Infections

In the pediatric study for cIAI there were 5 SAEs reported in 5 subjects in the AVYCAZ group including: ileus, intestinal obstruction, large intestinal perforation, renal colic, and vomiting. Per the FDA clinical reviewer (Dr. Gillian Taormina), renal colic (nephrolithiasis) was the only SAE included in the AVYCAZ labeling, occurring in <1% of adult subjects in phase 3 trials. The other SAEs were considered unlikely to be related to the study drug, but the role of AVYCAZ could not be excluded. There were four subjects with AESIs in the pediatric AVYCAZ group, one with diarrhea and three with hypersensitivity reactions including cough, pruritus, and rash. Per the clinical review for this study, cough, rash, and pruritus could have been hypersensitivity reactions related to AVYCAZ, although this was considered less likely in all three events, and there was no evidence of anaphylaxis. One subject in the AVYCAZ group developed a positive Coombs test which is a known effect of cephalosporins. There were no reports of symptomatic hemolytic anemia associated with Coombs seroconversion. There were no reports of liver or renal disorders. No children discontinued the study drug because of an adverse reaction or died during the study.

For the adult cIAI trials none of the AEs of death were considered by the FDA clinical reviewer (Dr. Benjamin Lorenz) to be related to study drug. The only SAEs considered related to AVYCAZ were hypersensitivity reactions. There were no cases of anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis. TEAE associated with AVYCAZ included diarrhea, vomiting, and nausea which were thought possibly due to metronidazole. Seroconversion from a negative to a positive direct Coombs' test occurred in 12.9% (31/240) of subjects receiving AVYCAZ. No subjects had an AE of hemolytic anemia.

Complicated Urinary Tract Infections

In the pediatric trial for cUTI there were no deaths or dose adjustments, but three subjects discontinued the study drug due to AEs. One subject reported an SAE of nonspecific neurological symptoms (tingling, numbness, and weakness) which resolved without intervention and may have been preexisting. Another subject had an increased rate of tachycardia following study drug infusion which resolved spontaneously. A third subject developed dizziness, nausea, and vomiting on Study Day 2. These events were considered unlikely to be related to AVYCAZ by the investigator or original FDA clinical reviewer (Dr. Taormina). There were 8 SAEs in the pediatric study, all of which were assessed as unlikely to be related to AVYCAZ. One subject developed nephrolithiasis (but had a prior history of kidney stones), and one subject reported neurological symptoms resulting in AVYCAZ discontinuation. There were 10 subjects with AESI in the pediatric AVYCAZ group: 5 with diarrhea (7.5%), 5 hypersensitivity reactions (7.5%) including 2 with cough and 3 with a rash; and 1 with elevated gamma-glutamyl transferase (GGT). It was considered possible that the hypersensitivity

reactions were due to AVYCAZ. There were no cases of anaphylaxis. It was unclear the role of AVYCAZ with the elevated GGT as this subject's GGT was elevated at the beginning of the trial. The subject did not meet Hy's Law criteria. No subjects were reported to have hematological or renal disorders. Two subjects had a Coombs test seroconversion but did not have symptomatic hemolytic anemia.

In the adult cUTI trials there were 3 deaths for which the FDA clinical reviewer (Dr. Edward Weinstein) felt there were reasonable alternative explanations for the fatal outcome other than exposure to the study drug. AEs leading to AVYCAZ discontinuation included diarrhea. The most common TEAEs were headache, diarrhea, nausea, and constipation. An emergent safety signal of nephrolithiasis was identified and added to the drug labeling. There were 9 events of urolithiasis (5 cases of nephrolithiasis; 2 kidney calculus; 1 ureteral calculus; 1 ureteric calculus) in trial D4280C00002/4. No Hy's Law cases were identified. A positive Coombs test was seen in 3.2% of subjects.

Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

The pediatric HABP/VABP database is limited with Study C3591025 being a phase 1 single-dose PK study. No deaths were reported. One SAE or acute respiratory failure was reported on Study Day 15 which was thought unrelated to the study drug. There were 3 AESIs including elevated ALT and AST and rash in a single subject. The AE of rash occurred around the time of AVYCAZ infusion and was assessed as mild and potentially related to the study drug. The elevated transaminases were thought unrelated to the study drug.

In the adult HABP/VABP trial neither the FDA clinical reviewer (Dr. Weinstein) nor investigator attributed any of the cases of death to AVYCAZ. Three subjects in the AVYCAZ group met the laboratory screening criteria for Hy's law but did not satisfy Hy's law due to concurrent medications as well as illnesses, such as septic shock or cholecystitis, all providing alternative explanations for the liver injury. Coombs test was positive in 21.4% of subjects receiving AVYCAZ with no associated cases of hemolytic anemia.

8.2.9. 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, a prolonged duration of exposure is not anticipated.

Human Reproduction and Pregnancy

There are no new studies on reproductive and developmental toxicology effects with AVYCAZ.

Pediatrics and Assessment of Effects on Growth

The study under review is a pediatric study. In this and prior pediatric studies, subjects 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 most frequently administered in a hospital setting making the possibility of overdose less likely.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Division of Pharmacovigilance (DPV) performs routine pharmacovigilance to monitor all adverse events associated with AVYCAZ. DPV reviewed all serious FDA Adverse Event Reporting System (FAERS) reports for AVYCAZ in pediatric patients through age 17 years with a period of search from February 25, 2015 (the date of AVYCAZ approval in the United States) through January 20, 2022. Thirty-seven reports of serious adverse events in pediatric patients were filed including 18 reports with the outcome of death. No new safety signals, no increased severity or frequency of any labeled adverse events were reported, and no deaths were directly associated with AVYCAZ. DPV's conclusion from their September 09, 2022, report was to continue standard monitoring of adverse events.

The overall safety and tolerability profile of AVYCAZ is well-characterized with a cumulative safety database as of February 24, 2022, in which it was estimated that 4,788 subjects had participated in the AVYCAZ clinical development program: 1,450 subjects were exposed to AVYCAZ alone; 1,067 subjects received AVYCAZ either in combination with metronidazole or in a cross-over design with other drugs (avibactam, ceftazidime, ceftaroline fosamil-avibactam, moxifloxacin); 29 subjects received placebo; and 2,242 subjects received comparator drugs.

The Applicant submitted a review of the Annual Periodic Adverse Drug Experience (ADE) Report from February 25, 2022, to February 24, 2023, which showed 186 reports describing 357 adverse events, including 266 serious adverse events (46 expected and 220 unexpected) and 91 nonserious adverse events. There were 35 reported cases with a fatal outcome. In 10 cases the cause of death was unknown, and 8 cases had insufficient information for a meaningful assessment. Seventeen cases reported a cause of death. All of the cases with a reported cause of death were confounded by the patients' underlying medical conditions and/or surgical procedures. No new safety concerns for AVYCAZ were identified.

A PubMed search by the clinical reviewer for "pediatric" and "ceftazidime-avibactam" did not yield any studies with new safety concerns.

No new safety signals were identified among the postmarketing data or review of the literature.

Expectations on Safety in the Postmarket Setting

AVYCAZ is currently on the market and based on review of the data in this submission, there are no expectations for the development of new safety issues if the approved indications are expanded to include infants less than 3 months of age.

8.2.11. Integrated Assessment of Safety

The assessment of safety of AVYCAZ in the neonate and infant population is limited to Study C3591024. The cumulative AVYCAZ safety database provided in the NDA includes 178 pediatric (<18 years) and 1,809 adult subjects enrolled across 4 clinical studies in pediatrics and 6 clinical trials in adults for the indications of cIAI, cUTI, or HABP/VABP. In Study C3591024, there were no deaths, study drug discontinuations, or SAEs attributed to AVYCAZ that did not have alternative etiologies as more likely explanations. There were 71 TEAEs reported in 23 subjects. The majority of TEAE were mild or moderate in severity. No hypersensitivity reactions were identified. There were no potential Hy's Law cases. There was 1 case of renal failure and 1 case of oliguria which were not attributed to AVYCAZ. No cases of hemolytic anemia were identified. Two subjects had AEs of oxygen saturation decrease. For one subject, the mild TEAE of oxygen saturation decrease was attributed to the study intervention by the investigator. The overall safety profile of AVYCAZ in neonates and infants from birth (gestational age ≥ 31 weeks) to 3 months of age appears similar to the pediatric population ≥ 3 month and adult populations with cIAI, cUTI, or HABP/VABP treated with AVYCAZ. No new safety signals were identified.

8.3. Statistical Issues

Study C3591024 was a descriptive study with a limited number of subjects and without a control group with the primary aim to evaluate the PK, safety, and tolerability of AVYCAZ in neonates and infants <3 months. Efficacy was a secondary endpoint in this study which was not designed or powered for hypothesis testing.

8.4. Conclusions and Recommendations

The reviewers conclude that in accordance with 21 CFR 314.55, the Applicant has submitted adequate evidence to recommend the approval of AVYCAZ as a safe and effective treatment for cIAI, cUTI, or HABP/VABP in neonates and young infants from birth (gestational age ≥ 31 weeks) to < 3 months (89 days). Based on similarities in PK, disease pathophysiology, and microbiology in both adults and pediatric subjects, Study C3591024 supports the extrapolation of efficacy of AVYCAZ from adults to neonates and infants < 3 months of age for the indications of treatment of cIAI, cUTI, or HABP/VABP. No new safety signals were identified in Study C3591024. The overall safety profile of AVYCAZ in neonates and infants from birth (gestational age ≥ 31 weeks) to 3 months of age appears similar to the pediatric population ≥ 3 month and adult populations with cIAI, cUTI, or HABP/VABP treated with AVYCAZ. This application fulfills PREA PMR 2862-03.

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting convened for this sNDA.

10. Pediatrics

AVYCAZ has previously been approved for use in pediatric patients aged 3 months to <18 years with cIAI, cUTI, and HABP/VABP. The current submission addresses the PK, safety, and tolerability for AVYCAZ in neonates and young infants from birth (gestational age ≥ 31 weeks) to <3 months (89 days). The FDA Pediatric Review Committee (PeRC) was consulted and agrees this application fulfills PREA PMR 2862-03. There are no outstanding PMRs.

The Division of Pediatric and Maternal Health (DPMH) was consulted for assistance with the review of pediatric labeling language included in the Prescribing Information (PI). DPMH participated in applicable team meetings to discuss the application and proposed labeling recommendations.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

This prescribing information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved). The finalized PI was compared to the currently approved PI and the Applicant's draft PI submitted on July 27, 2023 (see Table 26 below). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 26. Summary of Key Changes to the Prescribing Information

Full Prescribing Information Sections[1]	Rationale for Major Changes to the Finalized Prescribing Information (PI)[2] Compared to the last Approved PI
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	Under subsections *1.1 (cIAI),1.2 (cUTI, including pyelonephritis) and 1.3 (HABP/VABP)*: • Accepted Applicant's deletion of "age 3 months and older." • Revised the age group (adults and pediatric patients) proposed by the Applicant in the indication statement by adding the parenthetical statement "(at least 31 weeks gestational age)" so that the age group reads as "adult and pediatric patients (at least 31 weeks gestational age)." Refer to Section 6.1 of the Summary Review and the Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling (March 2019), https://www.fda.gov/media/84949/download for additional details.
2 DOSAGE AND ADMINISTRATION	Under subsection 2.2 *Recommended Dosage in Pediatric Patients:* • The Applicant's proposed dosage regimen for (b) (4) was limited to neonates with gestational age (GA) 31 weeks and older because the youngest GA enrolled in Study C3591024 was 31 weeks and there was a lack of PK and safety data below this GA. Refer to Sections 6.1 and 6.2 of the Summary Review for additional details. To better reflect the intended age range for the dosage and for consistency with the age demographics of the Study C3591024 patient population, the age range was revised in Table 2 of the PI to read as "Greater than 28 days to less than 3 months" and "Less than or equal to 28 days with GA 31 weeks and older" and a footnote was added to clarify dose eligibility in neonates and pre-term infants. Refer to Section 6.1 and 6.2.1 for additional details.
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	N/A

6 ADVERSE REACTIONS	Under subsection 6.1, *Clinical Trials Experience in Adult Patients* subheading • Deleted the phrase [redacted] from the adult clinical trials experiences for each of cIAI, cUTI, and HABP/VABP clinical trials as this phrase was considered by the clinical review team to be confusing. Under subsection 6.1, *Other Adverse Reactions of AVYCAZ and Ceftazidime in Adults* subheading • Deleted the statement '[redacted] from phase 3 trials laboratory changes in adults and renamed this section, "*Direct Coombs' Test Seroconversion with AVYCAZ*". This edit is consistent with FDA guidance on reporting [redacted] in Section 6.1 since these trials were not powered to evaluate [redacted] See Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, Guidance for Industry, January 2006, https://www.fda.gov/media/72139/download Under *Adverse Reactions with Ceftazidime, a subheading under Other Adverse Reactions of AVYCAZ and Ceftazidime in Adults* • Added to *Nervous systems disorders*" adverse reactions of "seizures, encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia" from the Adverse Reactions section of the FORTAZ labeling. • Renamed '[redacted]" to "*Hypersensitivity Reactions*" and added "anaphylaxis" as an adverse reaction to be consistent with the FORTAZ labeling. Under subsection 6.1, *Clinical Trials Experience in Pediatric Patients* subheading • The Applicant added a paragraph summarizing the safety findings from pediatric patients < 3 months of age enrolled in Study C3591024. The review team accepted the Applicant's addition with the following revisions: • Re-ordered clinical trials experience in pediatric patients to have subsections for 3 months to less than 18 years of age as well as less than 3 months of age. The less than 3 months of age section was revised to include the demographics safety data from the 25 patients receiving a single dose of AVYCAZ in Part A and the additional 21 patients receiving multiple doses of AVYCAZ in Part B. • The Applicant proposed adding the statement '[redacted] Based on the reviewer's analysis of TEAEs (see Section 8.2.4 of the Summary Review), the statement was revised to report adverse reactions occurring in greater than 3%

	of pediatric patients less than 3 months of age in Study C3591024: ○ Vomiting: this TEAE occurred in 3/46 (6.5%) of patients ○ Increased transaminases: 4 subjects (4/46; 8.7%) had 5 reported TEAEs [reported as events of 2 "hepatic enzyme increased"; 2 elevated "transaminases"; one "Alanine aminotransferase increase"]. • Added a subsection "6.2 Postmarketing Experience" to describe adverse reactions and altered laboratory tests that have been identified during post-approval use of ceftazidime (a component of AVYCAZ), or other cephalosporin-class antibacterial drugs. • This was based on the listed "Cephalosporin-Class Adverse Reactions" in the "Postmarketing Experience with FORTAZ Products" section in the FORTAZ labeling. This revision was also supported by the labeling recommendations in 21 CFR 201.57(c)(7)(i) that requires that Section 6 list the adverse reactions that occurred with the subject drug (in this case, AVYCAZ) and with drugs in the same pharmacologically active and chemically related class, if applicable (in this case, other cephalosporin-class antibacterial drugs). In addition, the listing of these adverse reactions under subsection 6.2, was based on 21 CFR 201.57(c)(7)(ii)(B) that recommends that the listing of adverse reactions from domestic and foreign spontaneous reports must be separate from the listing of adverse reactions identified in clinical trials,
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Under subsection 8.4 *Pediatric Use* • Revised the age group (pediatric patients) proposed by the Applicant in the pediatric use statement by adding the qualifying statement "at least 31 weeks gestational age and older" to read "The safety and effectiveness of AVYCAZ in the treatment of cUTI, cIAI, and HABP/VABP have been established in pediatric patients at least 31 weeks gestational age and older." • Revised [redacted (b) (4)] to "The safety and effectiveness of AVYCAZ in the treatment of cUTI, cIAI, and HABP/VABP have not been established in pediatric patients less than 31 weeks gestational age. Refer to Section 8.4 of the Summary Review and the Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling . https://www.fda.gov/media/84949/download, for additional details
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	N/A
12 CLINICAL PHARMACOLOGY	Under subsection 12.3 *Pediatric Patients* subheading • Changed age group for pediatric dosing regimen statement from [redacted (b) (4)] to "birth (with gestational age 31 weeks and older) to less than 2 years without renal impairment." Refer to Section 6.1 and 6.2.1 of the Summary Review for additional details.
13 NONCLINICAL TOXICOLOGY	N/A

14 CLINICAL STUDIES	The Applicant proposed [redacted] (b) (4) [redacted] The review team disagreed with the Applicant's revision as this [redacted] (b) (4) [redacted]. See the Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. Guidance for Industry January 2006. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-studies-section-labeling-human-prescription-drug-and-biological-products-content-and-format. [redacted] (b) (4) [redacted]
17 PATIENT COUNSELING INFORMATION	N/A
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Under section 16 *How Supplied/Storage and Handling* • Added a summary statement with a cross-reference to the detailed storage conditions for the constituted and diluted solutions in Section 2 according to best labeling practice.

Source: Generated by the FDA review team.
[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the currently approved PI and the applicant's draft PI).

Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information

12. 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.

13. Postmarketing Requirements and Commitment

The studies submitted in this sNDA are pediatric assessments intended to fulfill PMRs associated with the initial approval of AVYCAZ. There are no outstanding PMRs. No new PMRs will be issued with the approval of this sNDA.

14. Division Director (Clinical) Comments

I agree with the review team's assessment and recommendations.

15. Appendices

15.1. References

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15.2. Financial Disclosure

The Applicant has noted no investigators with financial arrangements, payments, or interests requiring disclosure under 21 CFR 54.4(a)(3) for Study C3591024; this is referenced on Form FDA 3454.

Covered Clinical Study (Name and/or Number): C3591024

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 37		
Number of investigators who are Applicant 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 Applicant 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.4.1. Summary of Bioanalytical Method Validation and Performance

A previously validated bioanalytical method was used for quantitation of CAZ and AVI in plasma PK samples obtained from Study C3591024. The accompanying validation and sample analysis reports have been reviewed and deemed acceptable. Details on bioanalytical method performance are summarized in Table 27 and Table 28 below.

Table 27. Bioanalytical Method Validation Summary

Validation report #	C3599002
Analytes	CAZ and AVI
Method of Detection	LC-MS/MS
Biological Matrix	Human plasma
Anticoagulant	Sodium Fluoride/Potassium Oxalate
Internal Standard(s)	Ceftazidime-d_6 and Avibactam-$^{13}C_5{}^{15}N$
Calibration Standard Range (µg/mL)	• CAZ: 50.0 – 100,000 ng/mL • AVI: 10.0 – 20,000 ng/mL
QC Range (µg/mL)	• CAZ: 150.0 – 80,000 ng/mL • AVI: 30.0 – 16,000 ng/mL
Highest Dilution QC	• CAZ: 218,000 ng/mL • AVI: 43,600 ng/mL
Inter-day Accuracy (%RE)	• CAZ: -0.4 to 1.3% • AVI: -7.3 to 12%
Inter-day Precision (%CV)	• CAZ: 3.4 to 7.0% • AVI: 3.7 to 12.3%
Intra-day Accuracy (%RE)	• CAZ: 2.7 to 7.8% • AVI: -0.8 to 1.0%
Intra-day Precision (%CV)	• CAZ: 1.3 to 7.8% • AVI: 2.8 to 4.9%
Storage Stability	• CAZ: 854 days at -70°C • AVI: 794 days at -70°C

Source: Generated by the FDA review team.

Table 28. In-Study Method Performance Summary for Study C3591024

Performance Parameter	Results
QC Range (µg/mL)	• CAZ: 50.0 – 80,000 ng/mL • AVI: 10.0 – 16,000 ng/mL
QC Inter-day Accuracy (%RE)	• CAZ: -1.6 to 1.3% • AVI: -1.3 to 1.3%
QC Inter-day Precision (%CV)	• CAZ: ≤ 8.2% • AVI: ≤7.2%
Incurred Sample Reanalysis (Percentage within ± 20%)	• CAZ: 79.2% • AVI: 100%

* Based on final results following troubleshooting of failed AVI ISR for Run 16 samples.
Source: Generated by the FDA review team.

Reviewer comment: *Because CAZ-AVI PK data from Study C3591024 provides key supportive information for the proposed dosage regimens in neonates and infants < 3 months of age, an*

Office of Study Integrity and Surveillance (OSIS) bioanalytical site inspection was requested (September 12th, 2023). In addition to the routine inspection, OSIS feedback was also requested on the acceptability of results stemming from sample re-assays conducted by the Applicant following their initial incurred sample reanalysis (ISR) assessment. OSIS declined the request for an on-site inspection, stating that the requested review goal date (January 15th, 2024) did not provide sufficient time for an inspection or remote regulatory assessment (RRR). In the response to the request, OSIS also noted that an RRR was last conducted at the analytical site in (b) (4) *during which 3 objectionable conditions noted below were identified:*

(1) (b) (4)

(2)

(3)

Following their review of the analytical site's written responses to these findings, OSIS recommended that the relevant review division for the impacted NDA consider evaluating the PK profile characteristics of samples from 2 specific subjects prior to including their data in calculations. All other data from the audited study were deemed reliable.

Based on the OSIS response to the consult request, the clinical pharmacology review of this submission focused on evaluating the acceptability of the results from samples that were re-analyzed following the ISR assessment. (b) (4) *. Therefore, the Applicant reanalyzed the impacted samples, all of which were obtained around Tmax and in the terminal phase. Using the sample re-assay results, ISR for AVI met the acceptance criteria; additionally, the re-assay and original results were within 20% of each other. The final reported concentrations represent the median AVI concentrations of the original and re-assay results unless the original value was confirmed, and thus reported instead. The rationale for the failure to meet ISR using the original sample run as reference is unclear. Nonetheless, the Applicant's handling of the re-analysis appears reasonable given that the original results did not deviate significantly from the re-assay results.*

15.4.2. Individual Study Review

Study C3591024

Study C3591024 was a Phase 2a, 2-part (single- and multiple-dose), open-label, non-randomized, multicenter study to assess the PK, safety, tolerability, and efficacy of CAZ-AVI in infants aged < 3 months and neonates with suspected or confirmed infections due to Gram-negative pathogens requiring IV antibiotics. Subjects were divided into 3 age-based cohorts and administered CAZ-AVI according to the weight-based doses summarized in Table 29.

The dosage regimens for this study were selected with the objective of achieving plasma exposures similar to those observed in adults receiving the therapeutic dose. The study originally intended to enroll 24 subjects divided evenly across the 3 cohorts in both Part A (single-dose) and Part B (multiple-dose) of the study. However, due to challenges with enrollment caused by the COVID-19 pandemic, the study was terminated after 25 and 21 subjects had undergone treatment in Parts A and B, respectively.

Table 29. Age Cohorts and Corresponding Ceftazidime-Avibactam Weight-Based Doses

Cohort	Age	CAZ-AVI weight-based dose	Infusion		
			Volume	Duration	Frequency
1	>28 days[a] to <3 months old	30 mg/kg CAZ 7.5 mg/kg AVI	Varies, will not exceed 2 mL/kg/dose	120 min	q8h (Part B Only)
2	GA ≥37 weeks and ≤28 days old	20 mg/kg CAZ 5.0 mg/kg AVI			
3	GA ≥26 weeks to <37 weeks and ≤28 days old	20 mg/kg CAZ 5.0 mg/kg AVI			

Source: Table 3 of Applicant's Individual Study Report for Study C3591024.
Note: Corrected age=Subtract the number of weeks born before 40 weeks of gestation from the chronological age or postnatal age (PNA). Corrected age was used only for determining eligibility of pre-term infants in Cohort 1. Actual age PNA) was used for determining eligibility of pre-term neonates in Cohort 3.
[a.] Includes term infants (gestational age [GA] ≥ 37 weeks > 28 days of age and pre-term infants with corrected age >28 days.

All enrolled subjects were included in the safety population. Overall, CAZ-AVI appeared to be well tolerated across all cohorts; the majority of TEAEs were considered mild to moderate in nature. Two subjects, both from Part B of Cohort 3, discontinued the study due to SAEs. For additional details on the safety and tolerability of CAZ-AVI in the clinical trial population, please see Section 8.2.

The PK analysis population, defined as subjects who received either a single IV dose in Part A or at least 3 consecutive doses in Part B, and had at least 1 CAZ and/or AVI plasma PK measurement available, was comprised of 45 of the 46 enrolled subjects. Three PK samples were planned for Study Day 1 (for Part A, the single-dose cohorts) or Study Day 2 to 14 (for Part B, the multiple-dose cohorts). In the single-dose cohorts, the schedule for PK sample collection (0.3 mL of blood per sample) was as follows: within 15 min, between 30 - 90 min and between 5 - 6 h post-infusion. In the event that all 3 samples could not be obtained (e.g., in subjects weighing < 1 kg), preference was given to the 1st and 3rd collection times. For the multiple dose cohorts, PK samples were obtained according to an identical sampling schedule after at least 3 consecutive doses had been administered. PK samples were analyzed using a previously validated bioanalytical method (see Section 15.4.1 for details on in-study method performance). PK data obtained from this study was used to update the existing population PK models for CAZ and AVI to predict drug exposures in infants < 3 months of age and neonates with cUTI, cIAI, and HABP/VABP. Notably, although Cohort 3 intended to enroll pre-term neonates with GA ≥26 weeks, the earliest enrolled GA was 31 weeks with a majority of the subjects in Cohort 3 born at GA of 31 to 33 weeks (i.e., 7 participants [87.5%] in Part A, and 5 participants [62.5%] in Part B).

The estimated mean steady state PK parameters from population PK analyses (based on individual post-hoc PK parameters) are summarized by cohort in Table 30. Mean CAZ and AVI

systemic exposures were ~20% lower for Cohort 2 (i.e., full-term neonates) than Cohorts 1 and 3. Nonetheless, due to the high intersubject variabilities, there is considerable overlap in exposures across cohorts (see Section 15.4.3 for additional details on exposure comparisons across the age range).

Table 30. Summary of Geometric Mean (%CV) of Ceftazidime and Avibactam PK Parameters Across Cohorts

Parameter	Cohort 1	Cohort 2	Cohort 3
N	16	12	16
Avibactam			
AUC_{SS0-24} (ug/mL•hr)	115 (35.8)	94.1 (62)	119 (99.6)
$C_{min,ss}$ (ug/mL)	0.75 (77.4)	1.05 (138)	2.07 (142)
$C_{max,ss}$ (ug/mL)	12.1 (29.8)	8.4 (48)	9.18 (95.7)
Ceftazidime			
AUC_{SS0-24} (ug/mL•hr)	626 (23.8)	505 (30)	653 (35.7)
$C_{min,ss}$ (ug/mL)	5.65 (74.8)	6.78 (73.4)	11.6 (83.7)
$C_{max,ss}$ (ug/mL)	61.4 (14)	43.6 (18)	50.4 (22.1)

Source: Table 2 of Applicant's Summary of Clinical Pharmacology Studies.

Reviewer comment: *The Applicant's overall findings from this study are consistent with the reviewer's analysis. It is worth noting that Cohort 1 enrolled both term and pre-term infants. For term infants, enrollment was based on having chronologic or postnatal age (PNA) > 28 days to < 3 months. The 28-day cutoff for Cohorts 2 and 3 were also based on postnatal age. However, for pre-term infants, enrollment in Cohort 1 was based on having a corrected age (which was determined by subtracting the number of weeks born before 40 weeks from the postnatal age of these infants) exceeding > 28 days. Additionally, Cohort 3 was unable to enroll pre-term neonates with GA ≥26 to 30 weeks, therefore, population PK modeling was used to estimate the expected exposures in these patients. See Section 15.4.3 for additional details.*

15.4.3. Pharmacometrics Review

15.4.3.1. Population PK Analysis

15.4.3.1.1. Review Summary

In general, the Applicant's population PK (PopPK) analysis is considered acceptable for the purpose of description of ceftazidime (CAZ)-avibactam (AVI) exposure in plasma of neonates and infants from birth to less than 3 months of age, and description of the effects of intrinsic and/or extrinsic factors on CAZ and AVI exposure. The Applicant's analyses were verified by the reviewer, with no discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 31.

Table 31. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	The recommended pediatric dosing regimens for patients from 2 to less than 18 years of age with eGFR of 50 mL/min/1.73 m^2 or higher and for patients from birth [gestational age (GA) at least 31 weeks] to less than 2 years without renal impairment are predicted to result in systemic exposures similar to that in adult patients given AVYCAZ 2.5 grams.	The statement is acceptable. Covariate analysis using the Applicant's final model demonstrates that **body weight** and a **renal maturation function** based on postmenstrual age (PMA) sigmoidal model were significant covariate for **pediatric patients ≤ 2 years of age.** As a result, dose adjustment as compared to older patients is recommended for pediatric patients < 3 months. In addition, based on population PK modeling and simulation, neonates with GA 26 to 30 weeks (assuming PMA and GA are equal) are predicted to have 30% to 60% higher exposure than older pediatric patients and adults, whereas neonates with GA of 31 weeks and older are predicted to have similar exposure as adults after administration of recommended dose for each age group. In addition, in Study C3591024, there were no pre-term neonates with GA < 31 weeks enrolled. Based on the above findings, the review team determined that the GA cut-off for use of the Applicant's proposed dosage regimen is 31 weeks and older.
Derive exposure metrics for exposure-response analyses	C_{min}, C_{max}, AUC		The predictive performance of the Applicant's updated population PK model was verified by goodness-of-fit (GOF) and visual predictive checks (VPC) plots (Figure 5 to Figure 8). The Applicant's final model is generally acceptable for generating exposure metrics for PTA analyses.

Source: Generated by the FDA review team.

15.4.3.1.2. Introduction

The primary objectives of the Applicant's analysis were to:

- To update the previously developed PopPK models for AVI and CAZ (reported in PMAR-1320) with a dataset that included additional individual plasma concentration data from neonates and infants from birth to less than 3 months of age from Study C3591024.
- To describe the pharmacokinetics (PK) of AVI and CAZ in neonates and infants from birth to less than 3 months of age by the estimation of secondary PK parameters for the subjects in Study C3591024.
- To assess, through PopPK simulations, the proposed pediatric dosing regimen for neonates and infants from birth to < 3 months old.

15.4.3.1.3. Model Development

(b) (4)

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(b) (4)

Applicant's Base Model

The base model for AVI proposed by the Applicant was a disposition model with first-order elimination from the central compartment following IV infusion. The base model for CAZ proposed by the Applicant was a 2-compartment disposition model with first-order elimination from the central compartment following IV infusion. The PopPK analysis was performed using nonlinear mixed effects modeling methodology as implemented in NONMEM TM (Version 7.5.0, ICON, Hanover, MD, USA).

Covariate Analysis

In accordance with the analysis plan, the following covariates were formally evaluated for AVI in NONMEM: body weight (WT), post-menstrual age (PMA), postnatal age (PNA), creatinine clearance normalized to 1.73 m^2 body surface area (nCrCL), end stage renal disease (ESRD), dialysis, population (cUTI, or cIAI adult Ph2 or cIAI/NP/cUTI), ventilator, acute physiology and chronic health evaluation (APACHEII) score. The following covariates were formally evaluated for CAZ in NONMEM: body weight, PMA, PNA, nCrCL, population (cUTI, or cIAI/NP), ventilator, race (Asian/Chinese/Japanese). Some of these covariates are not relevant for neonates or infants <3 months of age, but will be kept in the model, as the model aims to describe the PK from birth to adulthood. The impact of selected covariates on CL and Vc were tested in the model using a forward inclusion/backward elimination procedure, for which the minimal level of statistical significance required at the forward inclusion step was the $\alpha = 0.05$.

Refer to the Pre-Term Effect subsection below for a description of the age effect for neonates and infants 3 months of age.

Pre-Term Effect

The effect of the renal maturation process for subjects < 2 years old in the current models, is described by the sigmoid hyperbolic equation (Equation 1) originally proposed by Rhodin et al.

Equation 1. Sigmoid Hyperbolic Equation

$$maturation = \frac{PMA^{Hill}}{TM50^{Hill} + PMA^{Hill}} \quad (1)$$

Source: Rhodin et al, 2009, Human Renal Function Maturation: A Quantitative Description Using Weight and Postmenstrual Age, Pediatric Nephrology 24: 67-76, https://pubmed.ncbi.nlm.nih.gov/18846389/.

The maturation half-life (TM50) is fixed to the reported value of 47.7 weeks and the Hill exponent to the value of 3.4. Assuming that the time to reach 50% of the maximum renal maturation could be different in pre-term infants, a different value for TM50 could be estimated for pre-term neonates, if the current model does not describe this sub-group well.

The covariates that were included in the final AVI model were:

- PMA, ESRD, dialysis condition, nCrCL, population (cIAI), APACHE score effects on CL
- Population, ventilator and PMA, age (< 3 months versus ≥ 3 months) effects on Vc
- WT on Vp
- WT on Q

The covariates that were included in the final CAZ model were:

- PMA, WT, population (cIAI), race, nCrCL effects (age > 2 years) on CL
- WT, Population (cUTI, cIAI or HABP/VABP, and HABP/VABP), ventilator, race, pediatric (i.e., adult versus pediatric studies) effects on Vc

15.4.3.1.4. Applicant's Final Model

The parameter estimates for the final covariate model for AVI are listed in Table 37 and Table 38. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 5 and Figure 6. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in Figure 7 and Figure 8.

Table 37. Parameter Estimates (RSE) and Median (95% CI) for the Applicant's Final Model for AVI

Parameter	Estimate	RSE [%]	IIV [%]
θ_1: CL (L/h)	11.7	1.57	57.9
θ_2: Vc (L)	13.5	8.63	81.2
θ_4: Q (L/h)	7.69	21.5	205
θ_3: Vp (L)	8.13	7.72	110
θ_5: Relative est. ESRD patients CL ; CL x θ_5	0.0652	20.5	
θ_6: CL est. for dialysis patients (L/h)	23.2	6.98	
θ_7: Power nCrCL on CL	1.02	4.36	
θ_8: Linear nCrCL on CL	0.00335	11.5	
θ_9: Pop on Vc (cIAI) adult Ph2 (Vc x (1 + θ_9))	2.04	36.9	
θ_{10}: Pop on CL (cIAI) adult Ph2 (CL x (1 + θ_{10}))	0.442	38.5	
θ_{11}: Pop on Vc (cUTI) (Vc x (1 + θ_{11}))	0.536	22.2	
θ_{12}: Pop on Vc (cIAI adult Ph3 or cIAI ped or NP) (Vc x (1 + θ_{12})	0.349	28.0	
θ_{15}: APACHE on CL	-0.178	13.3	
θ_{28}: Ventilator on Vc	0.241	38.9	
θ_{38}: Age (<3m old) on Vc (Vc x (1 + θ_{38}))	0.772	26.6	
ω			Shrink. or corr. [a]
ω^2 CL	0.335	8.19	4.68
ω Vc-CL	0.152	17.1	0.323
ω^2 Vc	0.660	29.6	27.6
ω Vp-CL	0.573	28.9	0.900
ω Vp-Vc	-0.0702	102	-0.0785
ω^2 Vp	1.21	29.6	10.7
ω Q-CL	1.04	15.0	0.879
ω Q-Vc	-0.198	135	-0.119
ω Q-Vp	2.24	28.8	0.996
ω^2 Q	4.18	28.9	11.3
Residual Error			
θ_{17} Proportional variability Phase 1	0.175	8.02	
θ_{18} Additive variability Phase 1 (ng/mL)	44.7	22.9	
θ_{19} Proportional variability Phase 2	0.519	4.98	
θ_{20} Proportional variability Phase 3	0.389	4.49	

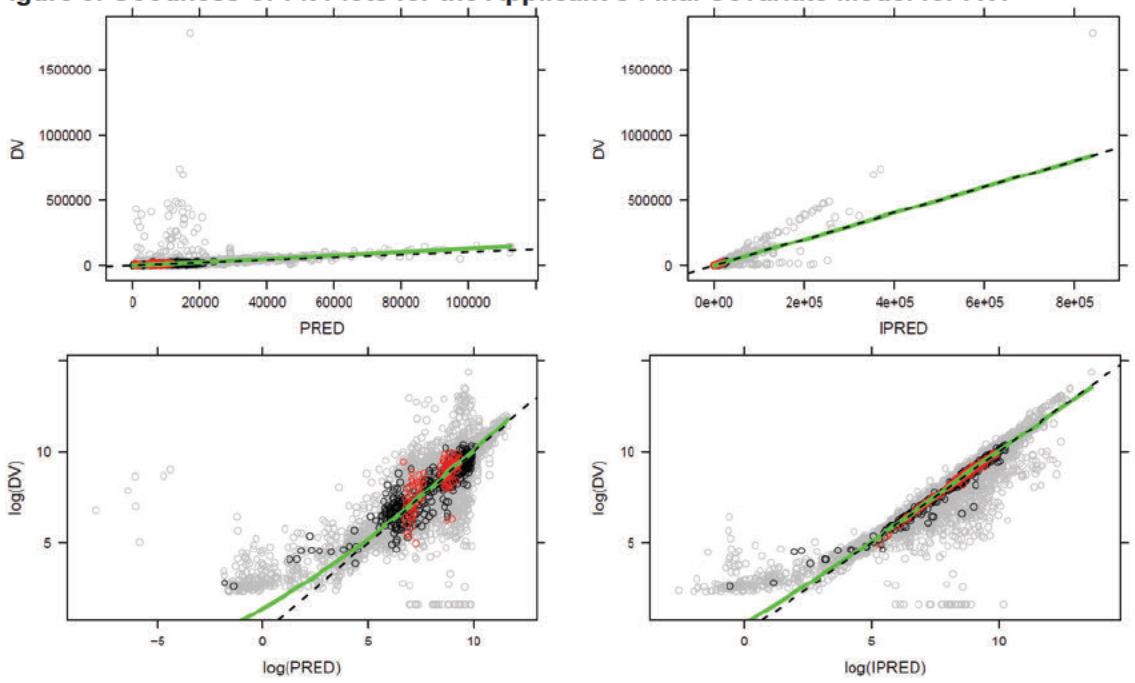
Source: Applicant's population PK report rd230648, Table 9.
[a.] Correlation coefficient (r) between random effects.
Abbreviations: AVI=Avibactam, PopPK=population pharmacokinetics, RSE=relative standard error, IIV=inter-individual variance, CL=clearance, Vc=central volume of distribution, Q=inter-compartmental clearance, Vp=peripheral volume of distribution, ESRD=end stage renal disease, nCrCL=creatinine clearance normalized to 1.73 m2 body surface area, q typical value of PK parameter, cIAI=complicated intra-abdominal infection , cUTI=complicated urinary tract infection, NP=nosocomial pneumonia.

Table 38. Parameter Estimates (RSE) and Median (95% CI) for the Applicant's Final Model for CAZ

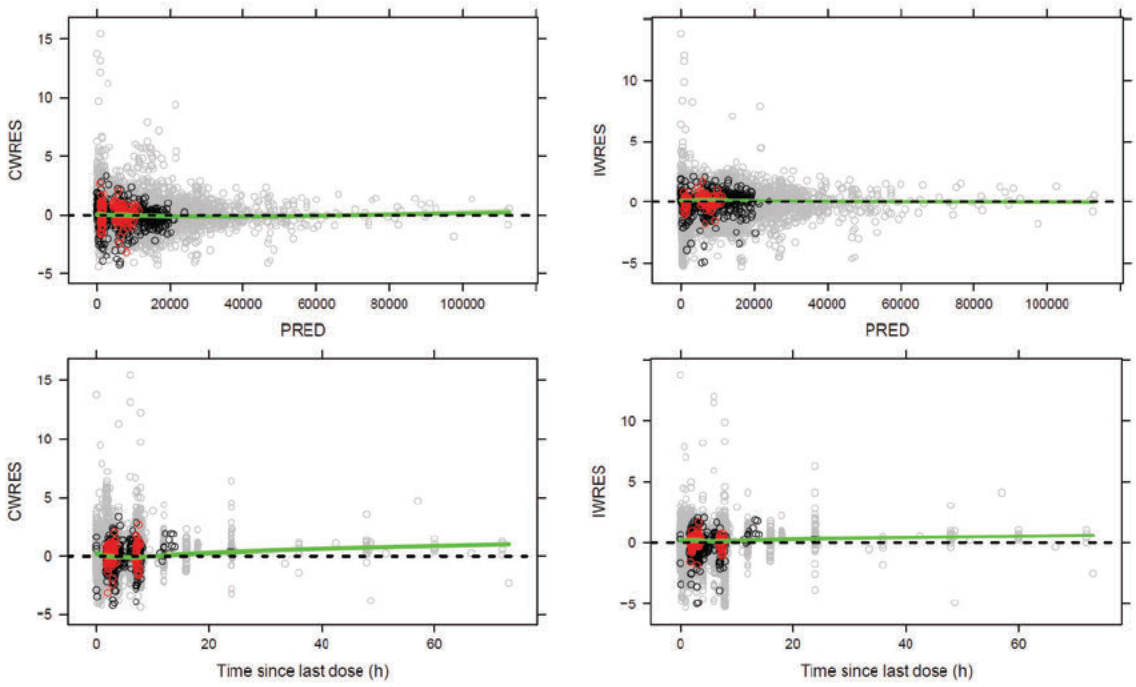
Parameter	Estimate	RSE [%]	IIV [%]
nCrCL effect on CL			
Slope 1: nCrCL < 100 mL/min; Slope 1 x nCrCL	0.01030360 Fixed		
Slope 2: nCrCL >= 100 mL/min; Slope 1 x 100 + Slope 2 x (nCrCL-100)	0.00125182 Fixed		
θ_1: CL (L/h)	7.75	31.8	39.3
θ_2: Vc (L)	11.2	3.52	32.9
θ_3: Q (L/h)	5.27	6.55	45.8
θ_4: Vp (L)	6.52	3.08	15.4
θ_{13}: Maximum covariate effect for WT on CL as an E_{max} function	1.64	32.0	
θ_{15}: WT at half-maximal effect of WT on CL as part of an E_{max} function	44.8	8.05	
θ_{16}: Population effect on CL for patients with cIAI (CL x θ_{16})	1.32	2.37	
θ_{17}: Population effect on CL for patients with NP (CL x θ_{17})	1.10	2.93	
θ_{18}: Race effect on CL for ASN (CL x (1 + θ_{18}))	-0.141	19.2	
θ_{19}: Race effect on CL for CHN (CL x (1 + θ_{19}))	-0.0930	26.0	
θ_{20}: Population effect on Vc for patients with cUTI (Vc x θ_{20})	1.50	4.57	
θ_{21}: Population effect on Vc for patients with cIAI or NP (Vc x θ_{21})	1.83	3.96	
θ_{22}: Population effect on Vc for presence of ventilator (Vc x (1 + θ_{22})	0.201	33.5	
θ_{23}: Race effect on Vc for ASN CHN and JPN (Vc x (1 + θ_{23}))	-0.138	22.3	
θ_{24}: Neonatal and infants <3 m on Vc (Vc x (θ_{24}))	1.68	9.29	
ω values			Shrinkage
ω^2 CL	0.154	5.13	10.4
ω^2 Vc	0.108	22.4	49.8
ω^2 Q	0.210	37.4	79.5
ω^2 Vp	0.0236	41.8	83.2
Residual Error			
Proportional variability Phase 1	0.172	10.4	
Additive variability Phase 1 (ng/mL)	125	16.2	
Proportional variability Phase 2 or 3	0.371	2.19	

Source: Applicant's population PK report rd230648, Table 9.
Abbreviations: RSE=relative standard error, IIV=inter-individual variance, nCrCL=creatinine clearance normalized to 1.73 m2 body surface area, q=typical value of PK parameter, CL=clearance, Vc=central volume of distribution, Q=inter-compartmental clearance, Vp=peripheral volume of distribution, WT=Body weight, cIAI=complicated intra-abdominal infection , cUTI=complicated urinary tract infection, NP=nosocomial pneumonia, ASN=Asian, CHN=Chinese, JPN=Japanese

Figure 5. Goodness-of-Fit Plots for the Applicant's Final Covariate Model for AVI



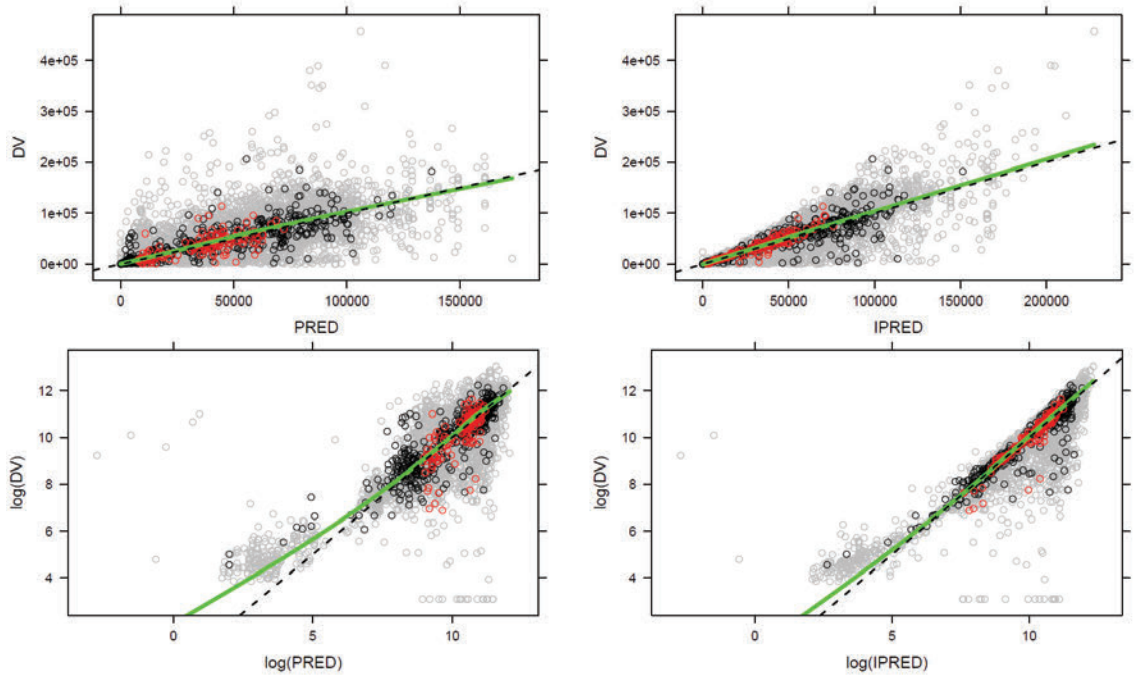
(a) FI-42683373



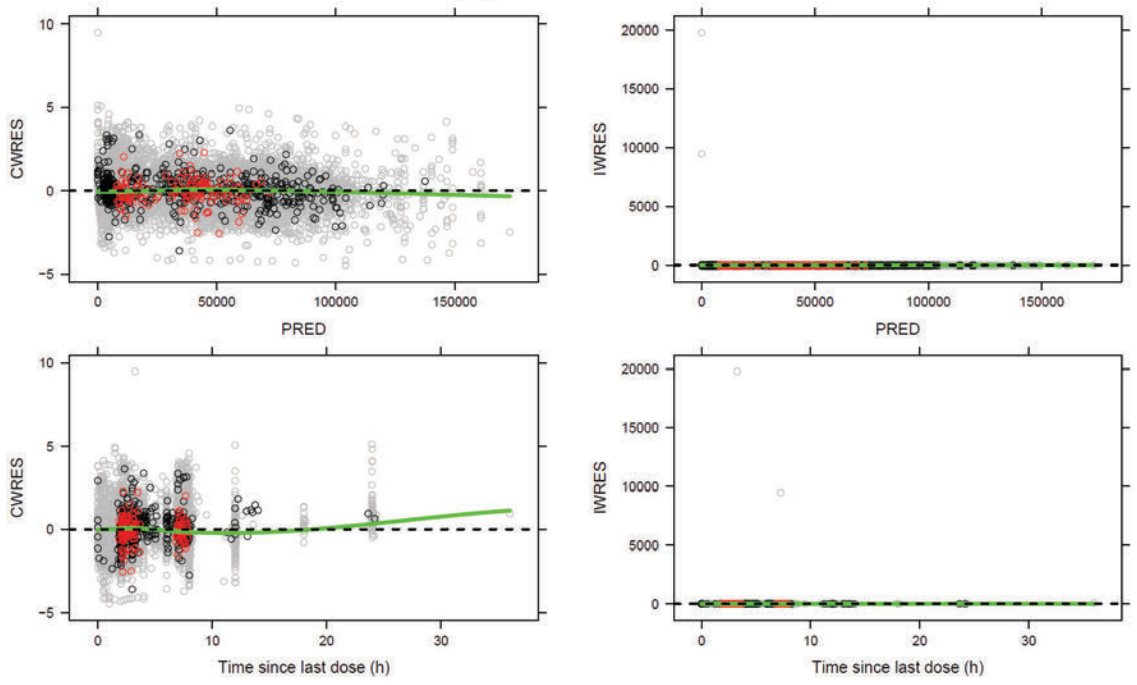
(b) FI-42683374

Source: Applicant's population PK report rd230648, Figure A5.6, Page 106.
Note: Each symbol represents an individual PK prediction (PRED, IPRED, CWRES, IWRES) and observation (DV). Gray circles represent adult patients/subjects while black circles represent pediatric patients, red circles represent pediatric subjects from Study C3591024. The solid green line is a loess to the data and the dashed line is the zero horizontal line (a) or the identity line (b). Outlier ID = (b) (6) excluded
Abbreviations: CWRES=conditional weighted residual, DV=dependent variable, IPRED=individual predictions, PK=pharmacokinetic, PRED=population predictions

Figure 6. Goodness-of-Fit Plots for the Applicant's Final Covariate Model for CAZ



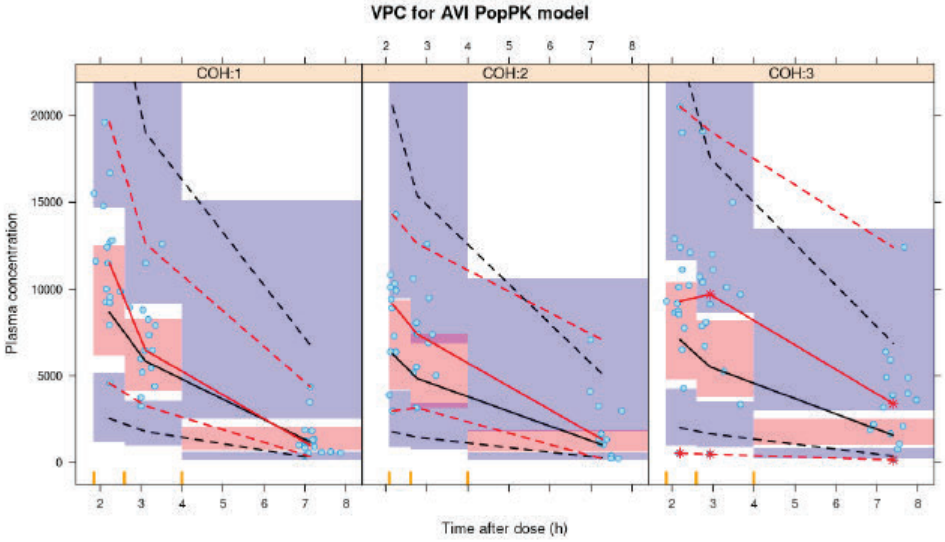
(a) FI-42726264



(b) FI-42817982

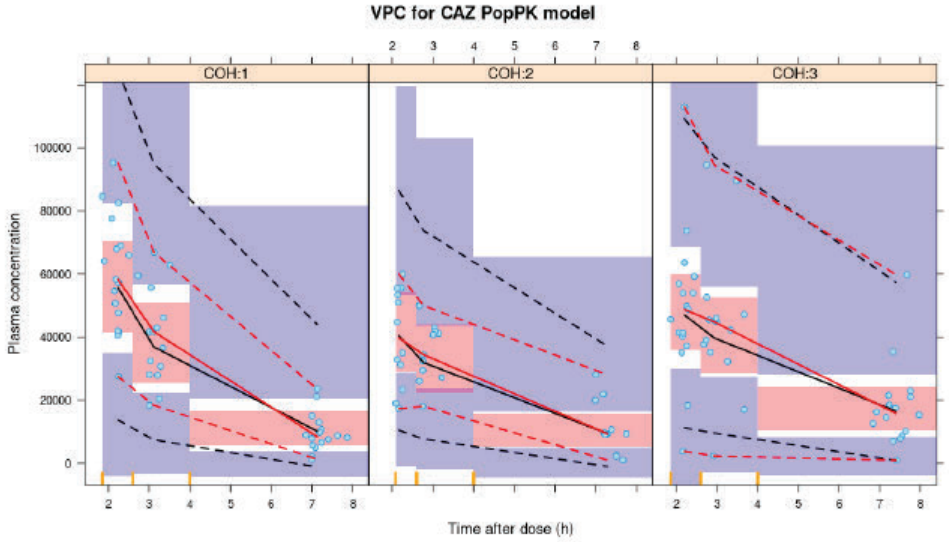
Source: Applicant's population PK report rd230648, Figure A5.18, Page 118.
Note: Circles represent adult patients/subjects gray), pediatric patients other than those from C3591024 (black , and pediatric subjects from Study C3591024 (red). The solid green line is a loess smooth of the data and the dashed line is the identity line (a) or a zero horizontal line (b). Outlier ID (b) (6) excluded.
Abbreviations: DV=dependent variable, PRED=population predictions, IPRED=individual predictions, CWRES=conditional weighted residual, IWRES=individual conditional residual

Figure 7. Visual Predictive Check (VPC) for AVI Final PopPK Model by Study Cohort



Source: Applicant's population PK report rd230648, Figure A5.10, Page 110.
Note: Each symbol represents an individual PK observation. The solid red line connects the median observed concentrations while the solid black line is the simulated median. The shaded region represents the 5th to 95th prediction interval for the median, 5th and 95th percentile based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black and observed (red) data.
Abbreviations: AVI=Avibactam, PopPK=population pharmacokinetics

Figure 8. Visual Predictive Check (VPC) for CAZ Final PopPK Model by Study Cohort



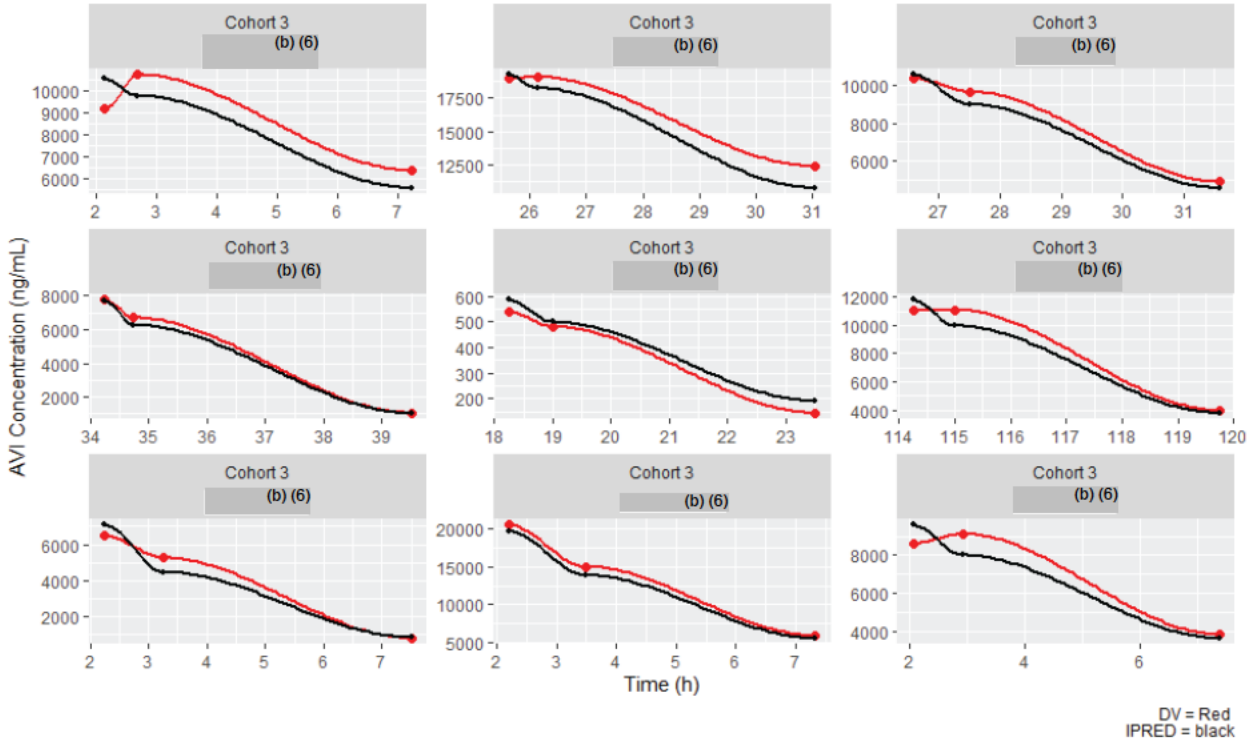
Source: Applicant's population PK report rd230648, Figure A5.22, Page 122
Note: Each symbol represents an individual PK observation. The solid red line connects the median observed concentrations while the solid black line is the simulated median. The shaded region represents the 5th to 95th prediction interval for the median, 5th and 95th percentile based on 1000 simulations. The dashed lines are the 5th to 95th prediction interval for the simulated (black) and observed (red) data.
Abbreviations: CAZ=Ceftazidime, PK=pharmacokinetics, VPC=visual predictive check

Reviewer comment: *Goodness-of -fit plots and VPCs for CAZ indicated that the present updated model adequately described the data from Study C3591024, and it was noted that ETA shrinkage values were reasonable. Therefore, the updated CAZ model was deemed to be acceptable for simulation purposes.*

The VPC plots for the AVI PopPK model show that there might be an underpredicting issue for pediatric patients with post-natal age (PNA) < 28 days (Cohort 2 and Cohort 3, Figure 7). Therefore, the reviewer conducted an analysis to check the individual prediction versus observed values for AVI data from Cohort 2 and Cohort 3. The GOF plot shows good agreement between IPRED and DV for pediatric patients < 3 months of age (red dot in Figure 9). Therefore, the review team also determined that the AVI model was deemed to be acceptable for simulation purposes.

For pediatric patients ≤ 2 years of age, the impact of renal maturation on CL was accounted for through application of a sigmoidal function of PMA in place of a CrCL effect (≥ 2 years of age) on CL. This approach is also considered to be appropriate.

Figure 9. Representative Plots for IPRED Versus DV in Cohort 3



Source: Reviewer's analysis.

Individual Drug Exposure Estimation

Model-based individual predictions for exposure parameters ($C_{max,ss}$, $C_{min,ss}$ and $AUC_{ss,\ 0\text{-}24}$) were estimated for the subjects in Study C3591024 and shown in Table 39. The results show that Cohort 3 has the higher $C_{min,ss}$ for both AVI and CAZ, being around double of the $C_{min,ss}$ of Cohort 1. On the other hand, $C_{max,ss}$ is higher on Cohort 1. $AUC_{ss,\ 0\text{-}24}$ is more similar between the 3 cohorts.

Table 39. Summary of Model Predicted $AUC_{ss,0-24}$, $C_{min,ss}$, $C_{max,ss}$ for AVI and CAZ in Study C3591024.

Parameter	Cohort 1	Cohort 2	Cohort 3
Number of subjects	16	12	16
AVI AUC_{ss0-24} (ug/mL*hr)	115 (35.9)	94.1 (62)	119 (99.6)
AVI $Cmin_{ss}$ (ug/mL)	0.75 (77.4)	1.05 (138)	2.07 (142)
AVI $Cmax_{ss}$ (ug/mL)	12.1 (29.8)	8.4 (48)	9.18 (95.7)
CAZ AUC_{ss0-24} (ug/mL*hr)	626 (23.8)	505 (30)	653 (35.7)
CAZ $Cmin_{ss}$ (ug/mL)	5.65 (74.8)	6.78 (73.4)	11.6 (83.7)
CAZ $Cmax_{ss}$ (ug/mL)	61.4 (14)	43.6 (18)	50.4 (22.1)
jPTA at T4 (percent of subjects)	100	100	94

Source: Applicant's population PK report, Table 12, Page 12.
Note: Values are the geometric mean (% CV).
Note: AUCss0-24 is obtained by multiplying $AUC_{ss,0-8}$ by 3. $C_{max,ss}$ is obtained at the end of infusion. $C_{min,ss}$ is obtained 8 hours after the start of infusion.
Abbreviations: $AUC_{ss,0-24}$=area under the plasma concentration-time curve over 24 hours at steady state, $C_{min,ss}$=minimum concentration at steady state, $C_{max,ss}$=maximum concentration at steady state, PTA=probability of target attainment
CAZ=Ceftazidime, AVI=Avibactam

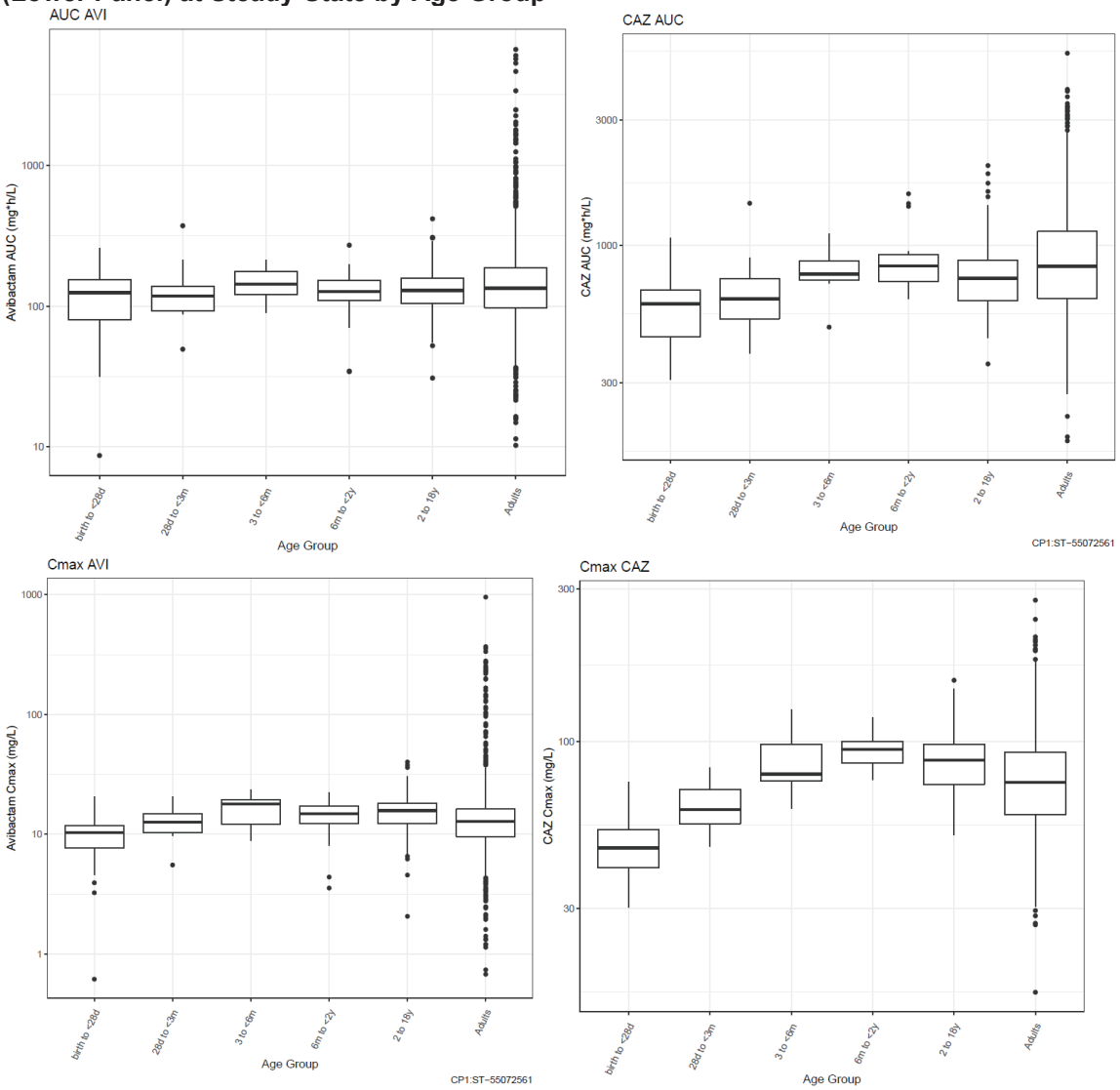
Reviewer comment: *In addition to the comparison for the PK parameters for AVI and CAZ in Study C3591024 across three cohorts, we were interested in knowing the estimated exposures of AVI and CAZ in pediatric patients < 3 months old as compared to older children and adults in clinical studies. Therefore, an information request was sent to the Applicant on 12/19/2023 requesting additional post-hoc cross-study comparison of AVI and CAZ exposures by age groups. The response was received on 01/03/2024 and 01/08/2024. All of the subjects included in this analysis received recommended dosing regimen as proposed in the USPI for their age group. The results were summarized in Table 40 and Figure 10.*

Table 40. Summary of CAZ-AVI Post-Hoc Pharmacokinetic Parameters at Steady-State by Age Group

Age group	Ceftazidime				Avibactam			
	N	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)	N	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)
Birth to ≤ 28 days	26	46.5, 46.4 (19)	10.5, 8.82 (79.7)	599, 568 (31.4)	26	10.3, 8.51 (75.6)	1.77, 1.47 (140)	124, 103 (81.4)
≥ 28 days to < 3 months	18	61.4, 61.6 (16.4)	6.24, 6.37 (91.8)	627, 649 (30.8)	18	12.7, 12.4 (31.4)	0.725, 0.875 (112)	118, 121 (45.3)
3 months to < 6 months	7	79.1, 85.5 (23.9)	5.43, 4.23 (72.9)	777, 778 (26.2)	7	18.0, 15.4 (36.7)	0.929, 0.836 (38.2)	143, 143 (30.8)
6 months to < 2 years	28	94.5, 93.2 (11.8)	4.36, 4.58 (89.7)	834, 848 (23.6)	28	14.9, 13.4 (44.9)	0.561, 0.533 (114)	127, 119 (48.2)
2 years to <18 years	123	87.7, 85.5 (22.6)	3.87, 4.06 (105)	748, 760 (32.1)	122	15.8, 14.9 (42.5)	0.531, 0.561 (91.8)	129, 129 (41.2)
≥ 18 years	1810	74.7, 74 (33.9)	10.8, 11.4 (113)	832, 858 (47.6)	1831	12.7, 12.8 (68.3)	1.35, 1.5 (133)	134, 141 (72.2)

Source: Applicant's IR response on 01/08/2024, Table 1, Page 6.
Note: Data presented as median, geometric mean (geometric CV%).

Figure 10. Boxplots of AVI (Left) and CAZ (Right) Post-Hoc $AUC_{ss,0-24}$ (Upper Panel) and $C_{max,ss}$ (Lower Panel) at Steady-State by Age Group



Source: Applicant's IR response on 01/08/2024, exposure_parameters_per_age_group-q2.pdf.

The results show that $AUC_{ss,0-24}$ and $C_{max,ss}$ for AVI were similar across the age groups, with considerable overlap in the median and interquartile range values. For CAZ, $C_{max,ss}$ and $AUC_{ss,0-24}$ were slightly lower in the neonatal group (birth to ≤ 28 days) compared to other age groups, but still within the range of adult values. It should be noted that since these post-hoc analyses were derived from clinical trial data, the gestational age range for the lowest age range group (birth to ≤ 28 days) was 31 weeks or above. There are no clinical data for pre-term neonates less than 31 weeks gestational age.

Simulated Drug Exposure and Joint PTA for Neonates and Infants <3 Months Old With cUTI, cIAI, or HABP/VABP

The AVI and CAZ final models have been used to simulate exposures and PTA for cUTI, cIAI and NP indications, extrapolating these effects to pediatric subjects <3 months of age from older

pediatric subjects and adults. Body weight and height distributions for pediatric patients ≤ 2 years old were derived from Centers for Disease Control and Prevention (CDC) growth charts or Olsen et al, 2010. For subjects > 2 years of age, covariates were re-sampled with replacement from the Applicant's internal covariate database comprising the CAZ-AVI and ceftaroline fosamil pediatric studies. The results are summarized in Table 41, Table 42, and Table 43.

Table 41. Summary of $C_{max,ss}$, $C_{min,ss}$, $AUC_{ss,0-24}$ and jPTA for the PKPD Target T4a at CAZ-AVI MIC of 8 mg/L in Pediatric and Adult Subjects With cUTI

Age Group	Dose[b] (CAZ/AVI)	CAZ $C_{max_{ss}}$ [mg/L]	CAZ $C_{min_{ss}}$ [mg/L]	CAZ AUC_{ss0-24} [mg.h/L]	AVI $C_{max_{ss}}$ [mg/L]	AVI $C_{min_{ss}}$ [mg/L]	AVI AUC_{ss0-24} [mg.h/L]	Joint PTA [%]
26 - <37w	20/5	58.7 (35.4)	26.1 (81.9)	990 (50.2)	7.22 (51.6)	2.5 (79.6)	112 (52.1)	99.1
0 - ≤4w	20/5	42.1 (20.9)	12.3 (65.7)	609 (31.6)	5.9 (50.9)	1.44 (78.7)	82.1 (47.1)	98.5
>4w - <3m	30/7.5	53.9 (20.3)	10.8 (82.5)	696 (31.8)	7.88 (51.4)	1.45 (92.8)	101 (46.9)	98.6
3 - <6m	40/10	76.1 (20.4)	4.37 (149)	736 (32.2)	11.6 (52.5)	0.649 (141)	114 (47)	95.2
6 - <12m	50/12.5	85.6 (20.5)	3.05 (172)	763 (31.4)	13.4 (52.1)	0.527 (160)	124 (46.6)	93.2
1 - <2y	50/12.5	81.3 (20.6)	2.28 (185)	697 (31.2)	13 (51.8)	0.444 (168)	118 (46.3)	89.3
2 - <6y	50/12.5	83.5 (22.3)	2.41 (189)	714 (32.5)	12.9 (52.5)	0.4 (169)	114 (46.2)	88.8
6 - <12y	50/12.5	91.6 (20.5)	5.02 (143)	862 (32.3)	13.8 (44.3)	0.752 (128)	133 (39.7)	96.2
12 - <18y	50/12.5	79.6 (24.2)	6.78 (103)	804 (33.2)	11.3 (68.5)	0.871 (90.1)	115 (53.9)	98.5
Adults	2000/500	74.4 (30.9)	9.22 (139)	823 (48)	10.1 (60)	1.1 (150)	112 (65.6)	96.9

Source: Applicant's population PK report, Table 13, Page 46.
Note: Pharmacokinetic parameter values correspond to geometric mean geometric CV% from 1000 simulated profiles per age group.
[a.] Target T4 was defined to be 50 % fT > MIC of 8mg/L for CAZ and 50% fT > CT of 1 mg/L for AVI.
[b.] Dose corresponds to mg/kg every 8 hours, except for the adults where dose corresponds to a fixed dose in mg. Pediatric maximum doses did not exceed adult dose.
Abbreviations: $C_{max,ss}$=maximum concentration at steady state, $C_{min,ss}$=minimum concentration at steady state, AUC_{ss0-24}=area under the plasma concentration-time curve over 24 hours at steady state, jPTA=joint probability of target attainment MIC=minimum inhibitory concentration, cUTI=complicated urinary tract infection, CAZ=Ceftazidime, AVI=Avibactam

Table 42. Summary of $C_{max,ss}$, $C_{min,ss}$, $AUC_{ss,0-24}$ and jPTA for the PKPD Target T4a at CAZ-AVI MIC of 8 mg/L in Pediatric and Adult Subjects With cIAI

Age Group	Dose[b] (CAZ/AVI)	CAZ $C_{max_{ss}}$ [mg/L]	CAZ $C_{min_{ss}}$ [mg/L]	CAZ AUC_{ss0-24} [mg.h/L]	AVI $C_{max_{ss}}$ [mg/L]	AVI $C_{min_{ss}}$ [mg/L]	AVI AUC_{ss0-24} [mg.h/L]	Joint PTA [%]
26 - <37w	20/5	45.8 (34.5)	18.5 (87.5)	748 (50.2)	7.47 (52)	2.33 (82.9)	112 (52.1)	98.5
0 - ≤4w	20/5	33.2 (20.7)	8.38 (72.1)	459 (31.6)	6.14 (51.4)	1.31 (82.4)	82.1 (47.1)	95.2
>4w - <3m	30/7.5	42.6 (20.3)	7.1 (92.7)	525 (31.8)	8.23 (51.8)	1.28 (98.1)	101 (46.9)	96.4
3 - <6m	40/10	60.7 (20.8)	2.41 (181)	556 (32.2)	12.1 (52.5)	0.543 (145)	114 (47)	87.3
6 - <12m	50/12.5	68.1 (21)	1.59 (211)	576 (31.4)	13.9 (52.1)	0.432 (163)	124 (46.6)	81.9
1 - <2y	50/12.5	64.5 (21.2)	1.17 (228)	526 (31.2)	13.5 (51.7)	0.363 (170)	118 (46.3)	72.6
2 - <6y	50/12.5	66.2 (22.8)	1.24 (233)	539 (32.5)	13.4 (52.2)	0.326 (171)	114 (46.2)	73.3
6 - <12y	50/12.5	72.7 (20.8)	2.82 (170)	651 (32.3)	14.4 (44.1)	0.635 (131)	133 (39.7)	89.8
12 - <18y	50/12.5	63.3 (24.3)	4.02 (119)	607 (33.2)	11.7 (68.6)	0.764 (89.5)	115 (53.9)	95.3
Adults	2000/500	58.1 (31.2)	5.56 (116)	601 (42.7)	10.3 (65.1)	0.818 (110)	105 (61.1)	94.8

Source: Applicant's population PK report, Table 14, Page 47.
Note: Pharmacokinetic parameter values correspond to geometric mean geometric CV% from 1000 simulated profiles per age group.
[a.] Target T4 was defined to be 50 % fT > MIC of 8mg/L for CAZ and 50% fT > CT of 1 mg/L for AVI.
[b.] Dose corresponds to mg/kg every 8 hours, except for the adults where dose corresponds to a fixed dose in mg. Pediatric maximum doses did not exceed adult dose.
Abbreviations: $C_{max,ss}$=maximum concentration at steady state, $C_{min,ss}$=minimum concentration at steady state, AUC_{ss0-24}=area under the plasma concentration-time curve over 24 hours at steady state, jPTA=joint probability of target attainment MIC=minimum inhibitory concentration, cIAI=complicated intra-abdominal infection, CAZ=Ceftazidime, AVI=Avibactam

Table 43. Summary of $C_{max,ss}$, $C_{min,ss}$, $AUC_{ss,0-24}$ and jPTA for the PKPD Target T4a at CAZ-AVI MIC of 8 mg/L in Pediatric and Adult Subjects With NP

Age Group	Dose[b] (CAZ/AVI)	CAZ $C_{max_{ss}}$ [mg/L]	CAZ $C_{min_{ss}}$ [mg/L]	CAZ AUC_{ss0-24} [mg.h/L]	AVI $C_{max_{ss}}$ [mg/L]	AVI $C_{min_{ss}}$ [mg/L]	AVI AUC_{ss0-24} [mg.h/L]	Joint PTA [%]
26 - <37w	20/5	52.4 (36.1)	24.7 (79.1)	903 (50.2)	8.13 (52.8)	1.94 (91)	112 (52.1)	99.1
0 - ≤4w	20/5	37.3 (21.2)	11.9 (62.8)	555 (31.6)	6.76 (52.3)	1.02 (90.7)	82.1 (47.1)	97.8
>4w - <3m	30/7.5	47.5 (20.5)	10.7 (78.2)	635 (31.8)	9.1 (52.5)	0.946 (110)	101 (46.9)	98.6
3 - <6m	40/10	67.6 (20.4)	4.4 (144)	672 (32.2)	13.2 (52.5)	0.353 (147)	114 (47)	94.7
6 - <12m	50/12.5	76.1 (20.5)	3.09 (168)	696 (31.4)	15.1 (52)	0.27 (162)	124 (46.6)	92.8
1 - <2y	50/12.5	72.4 (20.5)	2.31 (182)	636 (31.2)	14.6 (51.5)	0.226 (167)	118 (46.3)	88
2 - <6y	50/12.5	74.3 (22.2)	2.43 (183)	652 (32.5)	14.5 (51.7)	0.202 (169)	114 (46.2)	87
6 - <12y	50/12.5	81.2 (20.7)	5.01 (140)	787 (32.3)	15.7 (43.5)	0.426 (133)	133 (39.7)	96
12 - <18y	50/12.5	70.4 (24.3)	6.68 (101)	733 (33.2)	12.7 (68.4)	0.563 (84.5)	115 (53.9)	98
Adults	2000/500	63.8 (27.4)	7.79 (96.7)	699 (37.9)	11 (76.4)	0.8 (97.6)	109 (68.9)	96.3

Source: Applicant's population PK report, Table 15, Page 49.
Note: Pharmacokinetic parameter values correspond to geometric mean geometric CV% from 1000 simulated profiles per age group.
[a.] Target T4 was defined to be 50 % fT > MIC of 8mg/L for CAZ and 50% fT > CT of 1 mg/L for AVI
[b.] Dose corresponds to mg/kg every 8 hours, except for the adults where dose corresponds to a fix dose in mg. Pediatric maximum doses did not exceed adult dose.
Abbreviations: $C_{max,ss}$=maximum concentration at steady state, $C_{min,ss}$=minimum concentration at steady state, AUC_{ss0-24}=area under the plasma concentration-time curve over 24 hours at steady state, jPTA=joint probability of target attainment MIC=minimum inhibitory concentration, NP=nosocomial pneumonia, CAZ=Ceftazidime, AVI=Avibactam

Reviewer comment: *Since the population PK model used PMA as a covariate for CAZ and AVI CL for pediatric patients aged ≤ 2 years, the simulated exposures for CAZ and AVI was based on PMA age and respective dose levels as proposed in Table 33. In addition, to simplify the scenario, the PMA for pediatric patients was assumed to be equal to GA for pre-term neonates in the simulated population.*

Based on results from Table 41, Table 42, and Table 43, the predicted $AUC_{ss,0-24}$ from simulated pediatric patients less than 3 month of age were similar to those exposures in adult patients. For CAZ, the predicted $AUC_{ss,0-24}$ from simulated pediatric patients ranging in age from birth (PMA 26 weeks) to PNA < 3 months were similar to those exposures in adult patients. However, when the exposures for the different age cohorts within this simulated population were evaluated, the $AUC_{ss,0-24}$ of CAZ for premature neonates (PMA between 26 weeks to 37 weeks) were approximately 20% to 29% higher than those in adults, suggesting uncertainties of safety risks in pre-term neonates. As a result, an information request was sent to the Applicant on 12/19/2023 requesting analyses for simulated exposures of CAZ and AVI in two additional age sub-group: a) Pre-term neonates with postmenstrual age between 26 weeks and 30 weeks and b) pre-term neonates with postmenstrual age between 31 weeks to 37 weeks, as compared to adults with cUTI, cIAI, and NP. The response was received on 01/03/2024. The results are summarized in Table 44, Table 45, and Table 46.

Table 44. Updated Summary of $C_{max,ss}$, $C_{min,ss}$, $AUC_{ss,0-24}$ and jPTA for the PKPD Target T4a at CAZ-AVI MIC of 8 mg/L in Pediatric and Adult Subjects With cUTI

Age Group	Dose[b] (CAZ-AVI)	Ceftazidime			Avibactam			Joint PTA (%)
		$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)	
26 – 30 w[c]	20/5	70.6 (29.6)	38.7 (55.8)	1290 (39)	8.02 (49.9)	3.29 (64.1)	132 (48.8)	99.1
31 - <37 w[c]	20/5	50.6 (25.5)	19.7 (65)	809 (37)	6.67 (51)	2.07 (73.7)	99.8 (49)	98.9
0 - ≤4 w	20/5	42.1 (20.8)	12.2 (65.3)	608 (31.4)	5.9 (50.7)	1.44 (77.8)	82 (46.8)	98.1
>4w - <3m	30/7.5	54 (20.4)	10.9 (81.8)	698 (32)	7.89 (51.3)	1.45 (93.6)	101 (47)	98.6
3 - <6m	40/10	76.1 (20.1)	4.37 (146)	736 (31.6)	11.6 (52.4)	0.648 (140)	114 (46.7)	95.2
6 - <12m	50/12.5	85.8 (20.4)	3.08 (172)	766 (31.3)	13.4 (52.1)	0.53 (160)	125 (46.6)	93.3
1 - <2y	50/12.5	81.3 (20.7)	2.28 (186)	698 (31.3)	13 (52)	0.447 (169)	118 (46.7)	89.3
2 - <6y	50/12.5	83.4 (20.6)	2.46 (185)	716 (32.3)	12.7 (50.6)	0.43 (171)	114 (45.1)	88.8
6 - <12y	50/12.5	90.2 (21.9)	4.67 (143)	839 (31.2)	13.9 (50.1)	0.726 (124)	132 (45.2)	95.6
12 - <18y	50/12.5	79.8 (24)	6.96 (97.5)	810 (32.3)	11.4 (63.1)	0.91 (88.1)	116 (50.9)	98.8
Adults	2000/500	73.3 (30.4)	9.83 (139)	830 (48.7)	9.97 (67.2)	1.22 (172)	114 (76.2)	96.8

Source: Applicant's response to information request received on 01/03/2024 (SDN 600), Table 2, Page 9.
Note: Pharmacokinetic parameter values correspond to geometric mean (geometric CV% from 1000 simulated profiles per age group.
[a.] Target T4 was defined to be 50% fT>MIC of 8 mg/L for CAZ and 50% fT>CT of 1 mg/L for AVI.
[b.] Dose corresponds to mg/kg every 8 hours, except for the adults where dose corresponds to a fixed dose in mg. Pediatric maximum doses did not exceed adult dose.
[c.] Gestational age in pre-term neonates.
Abbreviations: $AUC_{ss,0-24}$=area under the concentration-time curve from time zero to 24 hr at steady-state, CAZ-AVI=ceftazidime-avibactam, $C_{max,ss}$=maximum concentration at steady-state, $C_{min,ss}$=minimum concentration at steady-state, m=month, PMA=postmenstrual age, PTA=probability of target attainment, w=week, y=year

Table 45. Updated Summary of $C_{max,ss}$, $C_{min,ss}$, $AUC_{ss,0-24}$ and jPTA for the PKPD Target T4a at CAZ-AVI MIC of 8 mg/L in Pediatric and Adult Subjects With cIAI

Age Group	Dose[b] (CAZ-AVI)	Ceftazidime			Avibactam			Joint PTA (%)
		$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)	
26 – 30 w[c]	20/5	54.8 (28.9)	28 (58.5)	974 (39)	8.27 (50.3)	3.1 (65.8)	132 (48.8)	99.1
31 - <37 w[c]	20/5	39.7 (25)	13.8 (69.9)	611 (37)	6.92 (51.5)	1.91 (76.7)	99.8 (49)	98.1
0 - ≤4 w	20/5	33.2 (20.6)	8.36 (71.6)	459 (31.4)	6.14 (51.2)	1.31 (81.4)	82 (46.8)	95.4
>4w - <3m	30/7.5	42.7 (20.3)	7.15 (91.8)	527 (32)	8.24 (51.7)	1.28 (99)	101 (47)	96.4
3 - <6m	40/10	60.7 (20.5)	2.41 (177)	556 (31.6)	12.1 (52.4)	0.542 (143)	114 (46.7)	87.8
6 - <12m	50/12.5	68.2 (20.9)	1.61 (212)	578 (31.3)	13.9 (52.1)	0.435 (163)	125 (46.6)	81.8
1 - <2y	50/12.5	64.5 (21.3)	1.17 (229)	527 (31.3)	13.5 (51.9)	0.365 (172)	118 (46.7)	73.2
2 - <6y	50/12.5	66.1 (21.1)	1.28 (228)	541 (32.3)	13.2 (50.4)	0.35 (173)	114 (45.1)	73.7
6 - <12y	50/12.5	71.6 (22.3)	2.61 (172)	633 (31.2)	14.5 (50)	0.612 (125)	132 (45.2)	88.8
12 - <18y	50/12.5	63.5 (24.2)	4.14 (112)	612 (32.3)	11.8 (63.1)	0.795 (87.4)	116 (50.9)	96.3
Adults	2000/500	57.6 (30)	5.66 (107)	599 (40.1)	10.2 (61.3)	0.821 (104)	104 (56.8)	95.1

Source: Applicant's response to information request received on 01/03/2024 (SDN 600), Table 3, Page 10.
Note: Pharmacokinetic parameter values correspond to geometric mean geometric CV% from 1000 simulated profiles per age group.
[a.] Target T4 was defined to be 50% fT>MIC of 8 mg/L for CAZ and 50% fT>CT of 1 mg/L for AVI.
[b.] Dose corresponds to mg/kg every 8 hours, except for the adults where dose corresponds to a fixed dose in mg. Pediatric maximum doses did not exceed adult dose.
[c.] Gestational age in pre-term neonates.
Abbreviations: $AUC_{ss,0-24}$=area under the concentration-time curve from time zero to 24 hr at steady-state, CAZ-AVI=ceftazidime-avibactam, $C_{max,ss}$=maximum concentration at steady-state, $C_{min,ss}$=minimum concentration at steady-state, m=month, PMA=postmenstrual age, PTA=probability of target attainment, w=week, y=year

Table 46. Updated Summary of $C_{max,ss}$, $C_{min,ss}$, $AUC_{ss,0-24}$ and jPTA for the PKPD Target T4a at CAZ-AVI MIC of 8 mg/L in Pediatric and Adult Subjects With HABP/VABP

Age Group	Dose[b] (CAZ-AVI)	Ceftazidime			Avibactam			Joint PTA (%)
		$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg.hr/L)	
26 – 30 w[c]	20/5	63.2 (30.1)	36.2 (54.4)	1180 (39)	8.94 (51.3)	2.67 (70)	132 (48.8)	99.1
31 - <37 w[c]	20/5	45 (26)	18.7 (62.5)	738 (37)	7.56 (52.4)	1.56 (83.6)	99.8 (49)	98.8
0 - ≤4 w	20/5	37.2 (21.1)	11.8 (62.4)	554 (31.4)	6.76 (52.1)	1.02 (89.6)	82 (46.8)	97.8
>4w - <3m	30/7.5	47.6 (20.6)	10.7 (77.5)	636 (32)	9.11 (52.3)	0.945 (111)	101 (47)	98.6
3 - <6m	40/10	67.5 (20.1)	4.4 (141)	671 (31.6)	13.1 (52.4)	0.351 (146)	114 (46.7)	94.5
6 - <12m	50/12.5	76.3 (20.4)	3.12 (168)	698 (31.3)	15.1 (52)	0.272 (162)	124 (46.6)	93.1
1 - <2y	50/12.5	72.4 (20.6)	2.32 (183)	636 (31.3)	14.6 (51.8)	0.227 (169)	118 (46.7)	88.9
2 - <6y	50/12.5	74.2 (20.5)	2.49 (181)	653 (32.3)	14.3 (49.9)	0.216 (172)	114 (45.1)	87.6
6 - <12y	50/12.5	80 (22.1)	4.67 (140)	765 (31.2)	15.8 (50)	0.41 (124)	132 (45.2)	95.2
12 - <18y	50/12.5	70.6 (24.1)	6.86 (95.1)	739 (32.3)	12.9 (63)	0.58 (82.5)	116 (50.9)	98.4
Adults	2000/500	62.7 (28.8)	7.63 (97.7)	686 (39.8)	10.6 (74)	0.81 (98.1)	106 (67.8)	96.1

Source: Applicant's response to information request received on 01/03/2024 (SDN 600), Table 4, Page 11.
Note: Pharmacokinetic parameter values correspond to geometric mean (geometric CV% from 1000 simulated profiles per age group.
[a.] Target T4 was defined to be 50% fT>MIC of 8 mg/L for CAZ and 50% fT>CT of 1 mg/L for AVI.
[b.] Dose corresponds to mg/kg every 8 hours, except for the adults where dose corresponds to a fixed dose in mg. Pediatric maximum doses did not exceed adult dose.
[c.] Gestational age in pre-term neonates.
Abbreviations: $AUC_{ss,0-24}$=area under the concentration-time curve from time zero to 24 hr at steady-state, CAZ-AVI=ceftazidime-avibactam, $C_{max,ss}$=maximum concentration at steady-state, $C_{min,ss}$=minimum concentration at steady-state, m=month, PMA=postmenstrual age, PTA=probability of target attainment, w=week, y=year

In this simulation, GA and PMA are used interchangeably, assuming PMA is equal to GA and PNA is 0 in these neonates. Based on these results, exposure was approximately 60% higher for CAZ and 30% higher for AVI for pre-term neonates with GA 26 to 30 weeks as compared to the age group of pre-term neonates with GA 31 to < 37 weeks. The exposure of CAZ and AVI in the age groups of pre-term neonates GA 31 to 37 weeks and full-term neonates are similar to that of adults. Considering the potential high exposure for pre-term neonates < 31 weeks GA and the lack of safety data from clinical trials in this age group, the review team determined that the age cut-off for this drug is GA 31 weeks and older.

Exposure- Response Analysis

PK/PD Target Attainment Analyses for Efficacy

The probability of target attainment (PTA) was determined for each subject in Study C3591024. The following joint target was used in the PTA analysis (corresponds to the target T4 in previous submission for infants ≥ 3 months): at least 50 percent of time of a dosing interval with a free drug concentration above the minimum inhibitory concentration (50% fT > MIC) of 8 mg/L for CAZ (in the presence of AVI) and a 50 percent of time of a dosing interval with a free drug concentration above concentration threshold (50% fT > CT) of 1.0 mg/L for AVI.

Subjects achieved the target if the fraction of the total dosing interval during which both AVI and CAZ concentrations were simultaneously above their respective concentration thresholds was greater than 50%. Free plasma concentration of ceftazidime and avibactam were calculated using unbound percentages of 85% and 92%, respectively.

The results of PTA analysis for the phase 2a population show that all cohorts have a very high joint PTA (>90%, Table 39) at the proposed dosing regimen. The PTA analysis in the simulated populations also show that all age groups corresponding to the 3 age cohorts in Study C3591024 achieved joint PTA similar to that achieved by adult subjects and are all >90%, independent of the indication being simulated (Table 41, Table 42, and Table 43).

Reviewer comment: *Based on the predicted pharmacokinetic concentration-time profiles, the joint 50 % fT > MIC (ceftazidime 8 mg/L) and 50 % fT > CT (avibactam 1 mg/L) target was achieved by all subjects in Cohorts 1 and 2, and 94% of subjects in Cohort 3 in Study C3591024 (Table 39). These results indicate that the proposed dose adjustment for infants < 3 months as compared to older patients is appropriate.*

Based on the above PK and PTA analysis, the final recommended dosing regimen for pediatric patients < 3 months of age is described in Table 47.

Table 47. The Final Recommended Dosage of AVYCAZ Ceftazidime and Avibactam) in Pediatric Patients Less Than 3 Months of Age

Infection	Age Range	Dose	Frequency	Infusion Time (hours)	Duration of treatment
cIAI*, cUTI including Pyelonephritis, and HABP/VABP	Less than or equal to 28 days[a] with GA 31 weeks and older	ceftazidime 30 mg/kg avibactam 7.5 mg/kg	Every 8 hours	2	cIAI: 5 to 14 days cUTI: 7 to 14 days HABP/VABP: 7 to 14 days
	Greater than 28 days[b] to less than 3 months	ceftazidime 20 mg/kg avibactam 5 mg/kg			

[a] Includes full-term infants with PNA > 28 days and pre-term infants with corrected age > 28 days. Corrected age is calculated by subtracting the number of weeks born before 40 weeks of gestation from the postnatal age.
[b] Includes neonates PNA ≤ 28 days and pre-term infants with corrected age ≤ 28 days. Abbreviations: GA=gestational age, PNA=postnatal ageSource: Reviewer's analysis.

15.5. Additional Clinical Trials Relevant to This NDA

Table 48 shows the phase 2 and 3 trials for cIAI, cUTI including pyelonephritis, and HABP/VABP in adults leading to approval of AVYCAZ for the treatment of susceptible gram-negative infections for these indications; along with the phase 1 (HABP/VABP) and phase 2 (cIAI and cUTI) studies in pediatric patients ages 3 months to less than 18 years which led to extension of AVYCAZ to the pediatric population 3 months to less than 18 years of age for these indications.

Table 48. Additional Studies to Support Safety or Efficacy in the Adult and Pediatric Populations

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Primary Study Endpoint	Treatment Duration/Follow-Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Controlled Studies in Adults to Support Efficacy and Safety								
D4281C00001	NCT01808092	Phase 3, Randomized, Multicenter, double-blind, actively controlled, noninferiority study for HABP/VABP in adults (REPROVE)	AVYCAZ (2.5g q8h administered IV over 120 min) Or Meropenem (1g q8h administered IV over 30 min)	28-Day all-cause mortality	Treatment: 7 to 14 days Final protocol follow-up on study Day 28	817 subjects (409 in the AVYCAZ group and 408 in the meropenem group)	Hospitalized patients with HABP/VABP aged 18 to 90 years	Study Sites 146 study sites Countries 24 countries
D4280C00006	NCT01644643	Phase 3, Open-label, randomized, multicenter study for treatment of infections due to ceftazidime-resistant gram-negative pathogens (REPRISE)	AVYCAZ 2500 mg IV over 120 minutes q8H or BAT	Proportion of patients with clinical cure at the TOC visit in the mMITT analysis set	Treatment 5 to 21 days Follow-up: cUTI 28-32 days cIAI 28-35 days after randomization	333 subjects (165 in AVYCAZ group and 168 in BAT)	Hospitalized adults aged 18 to 90 years with cIAI or cUTI due to CAZ-NS, gram-negative pathogens	Centers 53 centers Countries 16 countries

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Primary Study Endpoint	Treatment Duration/Follow-Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
D4280C00002/ 4	NCT01595438/ NCT01599806	Phase 3, randomized, multicenter, Double-blind Double-dummy, Parallel-group, comparative efficacy study in adults hospitalized with cUTI including AP (RECAPTURE)	AVYCAZ 2500 mg (2000 mg CAZ and 500 mg AVI) IV over 120 min q8H or Doripenem 500 mg IV q8H	Symptomatic and microbiological response	Minimum 5 days of IV therapy with option of oral switch (ciprofloxacin or sulfamethoxazole 800 mg/trimethoprim 150 mg twice daily or continuation of IV therapy for 10-day course (up to 14 days if subject is bacteremic at study entry) Follow-up: 45-52 days after randomization	1033 subjects (516 in AVYCAZ group and 517 in doripenem group)	Hospitalized adults aged 18 to 90 years suspected of having a cUTI due to a gram-negative pathogen	Centers 160 centers Countries 25 countries
D4280C00001/ 5	NCT01499290/ NCT01500239	Phase 3, Randomized, multicenter, Double-Blind, Double-dummy, Parallel-Group, comparative efficacy study in adults hospitalized with cIAI (RECLAIM 1/2)	AVYCAZ 2500 mg (2000 mg CAZ + 500 mg AVI) IV over 120 min, followed by metronidazole 500 mg IV over 1-hour q8H or meropenem 1000 mg IV q8H	Clinical response	Treatment: 5 to 14 days Follow-up: 42 to 49 days after start of study drug	1066 subjects (532 in AVYCAZ group; 534 in meropenem group)	Hospitalized adults aged 18 to 90 years with cIAI	Centers 136 centers Countries 30 countries
NXL104/2002	NCT00752219	Phase 2, Multicenter, Double-blind, randomized, comparative study for treatment of adults hospitalized with cIAI	AVYCAZ 2500 mg (2000 mg CAZ + 500 mg AVI) IV over 30 min + 500 mg MTX IV over 60 min q8H or meropenem 1000 mg IV over 30 min q8H	Clinical response; treatment emergent adverse events and serious adverse events	Treatment: 5 to 14 days Follow-up: 4 to 6 weeks post-therapy (up to 8 weeks	204 subjects (102 CAZ-1VI + MTX group and 102 meropenem group)	Hospitalized adults with cIAI	Study Sites 33 study sites Countries 8 countries

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Primary Study Endpoint	Treatment Duration/Follow-Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
NXL104/2001	NCT00690378	Phase 2, Multicenter, Investigator-blinded, randomized, comparative study for treatment of cUTI in adults	AVYCAZ 625 mg (500 mg CAZ + 125 mg AVI or Imipenem cilastatin 500 mg IV over 30 min q6H	Microbiological eradication	7 to 14 days total treatment with possible oral switch to ciprofloxacin after 4 days Follow-up: 4 to 6 weeks post-therapy	137 subjects 69 AVYCAZ group and 68 imipenem group)	Adults between ages 18 and 90 years with cUTI including acute pyelonephritis	Study Sites 26 study sites Countries 5 countries
Safety and PK Studies in Pediatric Patients 3 Months to 18 Years of Age								
C3591025	NCT04040621	Phase 1, Open label, single dose, PK, study in pediatric patients aged 3 months to <18 years	Subjects 6 to < 18 years of age and ≥ 40 kg: 2000 mg CAZ and 500 mg AVI Subjects 6 to < 18 years and <40 kg and all subjects 6 months to < 6 years: 50 mg/kg CAZ and 12.5 mg/kg AVI All subjects 3 months to < 6 months: 40 mg/kg CAZ and 10 mg/kg AVI Doses were to be halved for subjects with CrCl ≥ 30 to < 50 mL/min	PK	Single dose Late follow-up: 28 to 35 days after infusion	4 subjects	Hospitalized patients receiving systemic antibacterial therapy for suspected or confirmed NP, including VABP	Study Sites 4 study sites Countries 2 countries

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Primary Study Endpoint	Treatment Duration/Follow-Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
D4280C00015	NCT02475733	Phase 2, Randomized, multicenter, single-blind, safety, tolerability, and descriptive efficacy study in pediatric patients aged 3 months to < 18 years with cIAI	Patients 6 to <18 y ears and ≥ 40 kg: 2000 mg CAZ and 500 mg AVI Patients 6 months to < 18 years and < 40 kg: 50 mg/kg CAZ and 12.5 mg/kg AVI Patients 3 to < 6 months: 40 mg/kg CAZ and 10 mg/kg AVI All AVYCAZ doses were given as IV infusions over 120 minutes q8H; 10 mg/kg MTZ was administered over 20-30 minutes q8H after the AVYCAZ infusion AVYCAZ doses were to be halved for patients with CrCl > 30 to ≤ 50 mL/min	Safety and tolerability	Treatment minimum of 72 hours IV dosing with option to switch to oral therapy on Day 4 to 15 Late follow-up: 20 to 35 days from the last dose of study drug	83 subjects (61 in the AVYCAZ + MTX group and 22 in the meropenem group)	Hospitalized pediatric patients with cIAI aged 3 months to <18 years	Study Sites 29 study sites Countries 10 countries

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Primary Study Endpoint	Treatment Duration/Follow-Up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
D4280C00016	NCT02497781	Phase 2, Randomized, multicenter, single-blind safety, tolerability, and descriptive efficacy study in pediatric patients aged 3 months to < 18 years with cUTI	Patients 6 to < 18 years and ≥ 40 kg: 2000 mg CAZ and 500 mg AVI Patients 6 months to < 18 years and < 40 kg: 50 mg/kg CAZ and 12.5 mg/kg AVI Patients 3 to < 6 months: 40 mg/kg CAZ and 10 mg/kg AVI All doses were given as IV infusions over 120-minutes q8H Doses were to be halved for patients with CrCl >30 to ≤50 mL/minute	Safety and tolerability	Treatment minimum: 72h IV dosing, optional switch to oral therapy on Days 4 to 14 Late follow-up: 20 to 36 days after the last dose of study drug	97 subjects (68 in the AVYCAZ group and 29 in the cefepime group)	Hospitalized pediatric patients with cUTI aged 3 months to <18 years	Study Sites 25 study sites Countries 9 countries

Source: Generated by the FDA review team.
Abbreviations: AVI=Avibactam; BAT=best available therapy; CAZ=ceftazidime; AVYCAZ=ceftazidime-avibactam; cIAI=complicated intra-abdominal infection; CrCl=creatinine clearance; cUTI=complicated urinary tract infection; HABP=hospital-acquired bacterial pneumonia; IV=intravenous; mg/kg=milligram/kilogram; kg=kilogram mMITT=modified microbiological intent-to-treat; min=minutes; MTX=metronidazole; PK=pharmacokinetic s ; q8h=every 8 hours; TOC=test of cure; VABP=ventilator-associated bacterial pneumonia

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