NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	206494
Priority or Standard	Priority
Submit Date(s)	6/22/22
Received Date(s)	6/22/22
PDUFA Goal Date	12/22/22
Division/Office	CDER/OND/OID/DAI
Review Completion Date	
Established/Proper Name	Ceftazidime-avibactam
(Proposed) Trade Name	AVYCAZ
Pharmacologic Class	Cephalosporin (beta-lactam) and beta-lactamase inhibitor combination antibacterial drug
Code name	Not Applicable
Applicant	Allergan
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)	For the treatment of the following infections caused by designated susceptible gram-negative microorganisms: • Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in pediatric patients 3 months or older
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Not submitted
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of the following infections caused by designated susceptible gram-negative microorganisms: • Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in patients aged 3 months and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Nosocomial pneumonia (SCTID: 425464007) Ventilator-acquired pneumonia (SCTID: 429271009)
Recommended Dosing Regimen	Dosing based on age, weight, and renal function; see review for details

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DPMH= Division of Pediatrics and Maternal Health (DPMH)

Signatures

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Glossary

AC	Advisory committee
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BA	Bacteremia
BIMO	Bioresearch monitoring
BLA	Biologics license application
BNP	Brain natriuretic peptide
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit risk framework
CAP	Community-acquired pneumonia
CDAD	*C. difficile*-associated diarrhea
CDER	Center for Drug Evaluation and Research
CDTL	Cross-discipline team leader
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
cIAI	Complicated intra-abdominal infection
CMC	Chemistry, manufacturing, and controls
CNS	Central nervous system
CrCl	Creatinine clearance
CRE	Carbapenem-resistant Enterobacterales
CRF	Case report form
CRT	Clinical review template
CSR	Clinical study report
cUTI	Complicated urinary tract infection
DAI	Division of Anti-Infectives
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESBL	Extended-spectrum β-lactamase
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	Good clinical practice

GGT	Gamma-glutamyl transferase
HABP	Hospital-acquired bacterial pneumonia
IDSA	Infectious Diseases Society of America
IND	Investigational new drug
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intent to treat
LFU	Late follow-up
LRTI	Lower respiratory tract infection
MDR	Multidrug resistant/resistance
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
mITT	Microbiological intent-to-treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSP	Moderate-to-severe pneumonia
NDA	New drug application
NME	New molecular entity
NP	Nosocomial pneumonia
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PI	Prescribing information
PICU	Pediatric intensive care unit
PK	Pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PPI	Patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PT	Preferred term
PTA	PK/PD target attainment
REMS	Risk evaluation and mitigation strategy
RTI	Respiratory tract infection
SAE	Serious adverse event
SAP	Statistical analysis plan
SI	Serious infection
SOC	System organ class
TEAE	Treatment emergent adverse event
TOC	Test of cure
VABP	Ventilator-associated bacterial pneumonia

1 Executive Summary

1.1. Product Introduction

Ceftazidime-avibactam (CAZ-AVI; AVYCAZ®) is a fixed combination antibacterial drug product composed of ceftazidime, a third-generation cephalosporin, and avibactam, a non-β-lactam β-lactamase inhibitor, at a ratio of 4:1. Ceftazidime was first approved in 1985 (FORTAZ®, NDA 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. Avibactam is a beta-lactamase inhibitor that does not have antibacterial activity at the labeled dose, but rather protects ceftazidime from degradation by a range of bacterial beta-lactamase enzymes (Ambler Class A, Class C, and some Class D β-lactamase enzymes).

AVYCAZ was initially approved in February 2015 for the treatment of adults with complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in patients with limited or no alternative treatment options. Due to the limited clinical data submitted in the original application, the drug was approved with a statement of limited use. Two subsequent efficacy supplements provided clinical trial data in adult patients to support the removal of the limited use statements. The efficacy supplement for cIAI was approved on June 22, 2016 (Supplement 2) and cUTI on January 26, 2017 (Supplement 3). An additional efficacy supplement to support an indication for treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adult patients was approved on February 1, 2018 (Supplement 4). The dosing of AVYCAZ is the same across indications for patients aged 18 years and older, namely 2.5 grams (ceftazidime 2 grams and avibactam 0.5 grams) every 8 hours by intravenous (IV) infusion over 2 hours. The dose is modified for patients with impaired renal function. Efficacy supplements 5 and 6 were subsequently submitted to extend the indications for treatment of cUTI and cIAI to pediatric patients ≥3 months of age. These were approved on March 14, 2019 and fulfilled PMRs 2862-1 and 2862-2.

This efficacy supplement (Supplement 11) proposes to add a new population, treatment of HABP/VABP in pediatric patients aged ≥3 months to <18 years. The supplement was submitted in response to the Pediatric Research Equity Act (PREA) post marketing requirement (PMR) 2862-6 for AVYCAZ. The Sponsor planned to conduct a multicenter, open-label single-dose PK study enrolling approximately 32 hospitalized pediatric patients aged 3 months to less than 18 years who were receiving systemic antibacterial therapy for suspected nosocomial pneumonia. The AVYCAZ dosing in the study was the same as the approved dose for the pediatric cUTI and cIAI indications. However, due to recruitment challenges that were worsened by the COVID-19 pandemic and the European Medicines Agency (EMA) approval of a pediatric HABP/VABP indication for AVYCAZ, the Sponsor was only able to enroll 4 patients. In response to a Type C meeting request seeking guidance on a path for potential U.S. approval of an AVYCAZ pediatric

HABP/VABP indication, the Division of Anti-Infectives (DAI) recommended submitting a pediatric assessment in an efficacy supplement including updated population PK models, simulations, and probability of target attainment analyses to support the proposed dose of AVYCAZ in pediatric patients with HABP/VABP. The pediatric assessment including the population PK models and analyses have been submitted as part of this NDA supplement and is reviewed in detail below.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness to support the approval of AVYCAZ for treatment of HABP/VABP caused by susceptible gram-negative microorganisms in pediatric patients aged ≥3 months to <18 years was extrapolated from the adult HABP/VABP study (Study D4281C00001), as the pathophysiology of HABP/VABP and the responsible pathogens are similar in both populations. Population PK models, simulations, and probability of target attainment analyses of the proposed pediatric dosing for treatment of HABP/VABP provide additional supportive data (see Section 6.2 for additional details).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ceftazidime-avibactam (CAZ-AVI; AVYCAZ®) is FDA approved for the treatment of cIAI and cUTI in adults and pediatric patients ≥3 months of age, as well as treatment of HABP/VABP in adults. This efficacy supplement proposes to extend the HABP/VABP indication to pediatric patients aged ≥3 months to <18 years. The dosing regimen for all pediatric indications is age and weight-based, administered every 8 hours for 7 to 14 days by intravenous (IV) infusion over 2 hours.

The HABP/VABP patient population is characterized by comorbid conditions such as respiratory failure, sepsis, and multi organ failure, which confer a significant risk of death. HABP/VABP are common nosocomial infections in the US and may be associated with increased length of hospital stay, significant financial burden, and mortality rates of up to ~70% in certain populations. Although the incidence of HABP/VABP among pediatric patients appears to be lower than that in adults, they are still considered serious and life-threatening infections, especially among young children and infants. The risk of mortality is also greater in patients infected with multidrug resistant (MDR) pathogens, which are more common in HABP/VABP compared to community-acquired pneumonia.

Treatment options for HABP/VABP are limited when infections are caused by MDR pathogens such as carbapenem-resistant Enterobacterales (CRE) and extended-spectrum β-lactamase (ESBL)-producing organisms. The addition of avibactam restores ceftazidime's activity against gram-negative bacteria that express some of these β-lactamases. For the pediatric population, treatment options for MDR pathogens are even more limited and in some instances, no safe or effective treatment options exist. Therefore, the addition of CAZ-AVI to the pediatric armamentarium against HABP/VABP may provide substantial clinical benefits.

Study C3591025 was designed with a planned enrollment of 32 pediatric patients aged 3 months to <18 years and a primary objective of evaluating the PK of CAZ-AVI in pediatric patients with HABP/VABP. However, due to recruitment challenges that were worsened by the COVID-19 pandemic and the European Medicines Agency approval of a pediatric HABP/VABP indication for AVYCAZ, the Sponsor was only able to enroll 4 subjects between the ages of 11 months and 9.4 years. As only four subjects were enrolled in Study C3591025, additional safety data from the pediatric cIAI/cUTI studies and adult HABP/VABP studies were also reviewed. The safety profile of CAZ-AVI in Study C3591025 was similar to that in pediatric patients with cUTI and cIAI as well as adults with HABP/VABP. No unlabeled safety signals were reported in this study and there were no deaths. Key safety concerns for CAZ-AVI include *C. difficile*-associated diarrhea (CDAD), hypersensitivity reactions, and seizure, all of which appear as warnings in the product labeling and are known class effects of cephalosporins.

No efficacy data were analyzed in pediatric Study C3591025, as it was a single-dose study. Based on similarities in PK, HABP/VABP pathophysiology, and microbiology in adults and pediatric patients, efficacy data from Study D4281C00001 (a phase 3 pivotal study demonstrating the safety and efficacy of CAZ-AVI in the treatment of adult patients with HABP/VABP) were used to extrapolate evidentiary support for the proposed indication of treatment of HABP/VABP in pediatric patients aged ≥ 3 months to <18 years. Study D4281C00001 showed CAZ-AVI to be non-inferior to meropenem in the treatment of adult patients with HABP/VABP with respect to 28-day all-cause mortality in the intent-to-treat (ITT) population (CAZ-AVI mortality 9.6%, meropenem 8.3% [difference 1.48%; 95% CI: - 2.38 to 5.33]).

Overall, CAZ-AVI has a favorable safety and efficacy profile for the treatment of HABP/VABP in pediatric patients aged ≥3 months to <18 years. The risks associated with CAZ-AVI use in the pediatric population can be adequately addressed through the product labeling and routine postmarketing surveillance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The HABP/VABP patient population is characterized by comorbid conditions of respiratory failure, sepsis, and multi-organ failure. The risk of mortality is greater in patients infected with multidrug resistant pathogens.	Pathogens with resistance to multiple classes of existing antibacterial drugs (MDR) are associated with an increased risk of treatment failure and death.
Current Treatment Options	• This sNDA is for the treatment of HABP/VABP in pediatric patients aged 3 months to <18 years caused by susceptible gram-negative pathogens. • There are currently limited options for the treatment of HABP/VABP due to ESBL-producing pathogens, CREs and *Pseudomonas aeruginosa*. • The addition of avibactam restores ceftazidime's activity against gram-negative bacteria that express certain ESBLs, AmpC cephalosporinases, and serine carbapenemases.	There are limited treatment options for HABP/VABP due to MDR organisms, especially among pediatric patients. Salvage therapies risk significant toxicities. The existing armamentarium of drugs is expected to decline in utility over time due to the emergence and spread of MDR organisms, particularly carbapenemase-producing gram-negative pathogens.
Benefit	• The pediatric HABP/VABP study (Study C3591025) was a single-dose PK study; therefore, efficacy of CAZ-AVI was extrapolated from the adult HABP/VABP study (D4281C00001). • In the adult study, CAZ-AVI was non-inferior to meropenem in the	Based on similarities in PK, HABP/VABP pathophysiology, and microbiology in both adults and pediatric patients, efficacy data from Study D4281C00001 were used to extrapolate evidentiary

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment of patients with HABP/VABP with respect to 28-day all-cause mortality in the ITT population (CAZ-AVI mortality 9.6%, meropenem 8.3% [difference 1.48%; 95% CI: - 2.38 to 5.33]). • Resistance due to certain pathogen phenotypes, such as carbapenemase-producing *Klebsiella pneumoniae*, is as an area of unmet medical need. CAZ-AVI has the potential to address this need based on in vitro testing and animal model studies, but CAZ-AVI has yet to be tested in a controlled clinical trial against these specific pathogens.	support for the proposed indication of treatment of HABP/VABP in pediatric patients aged ≥3 months to <18 years.
Risk and Risk Management	• Key safety concerns for CAZ-AVI include *C. difficile*-associated diarrhea (CDAD), hypersensitivity reactions, and seizure, all of which appear as warnings in the product labeling. • The safety database for the pediatric HABP/VABP indication consists of the current pediatric HABP/VABP study (C3591025), as well as the adult HABP/VABP study (D4281C00001) and pediatric studies C3591005 (cUTI) and C3591004 (cIAI); the overall safety profile in the pediatric HABP/VABP patients treated with CAZ-AVI appears similar to that observed in the adult HABP/VABP patients as well as pediatric cUTI and cIAI patients. • Review of the current pediatric HABP/VABP study data as well as routine post-market safety monitoring have not revealed additional safety signals.	No unexpected safety signals were identified in the pediatric HABP/VABP patient population. The current labeling adequately informs the benefits and risks of AVYCAZ use.

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

Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are closely related infections of the lung parenchyma involving similar pathogens, and are subcategories of nosocomial pneumonia (NP). HABP is defined as a bacterial pneumonia that begins more than 48 hours after hospital admission or within 7 days after hospital discharge. When a bacterial lung infection arises in a patient who has been intubated for more than 48 hours, it is referred to as VABP. HABP/VABP are common nosocomial infections in the US[1] and have been associated with increased length of hospital stay, significant financial burden, and mortality rates in the range of 8 – 71%.[2,3,4,5]

Although the incidence of HABP/VABP among pediatric patients appears to be lower than that in adults, studies have reported incidence rates of up to 12% among pediatric patients hospitalized with pneumonia and slightly higher rates among neonates and infants. However, as a definitive diagnosis can be difficult to make and the clinical definitions of HABP/VABP differ between adult and pediatric populations, this number may be underestimated.[6]

The risk for mortality is greater for patients infected with multidrug resistant (MDR) pathogens. Several factors have been associated with the acquisition of MDR pathogens, such as previous antibacterial drug use within 90 days, septic shock, greater than 5 days of hospitalization, and acute renal failure with renal replacement therapy.[7]

An infection of the lungs is typically associated with clinical signs and symptoms of fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea, and the presence of a new or progressive infiltrate on a chest radiograph. Although less common than

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[1] Guillamet et al. (2015). Ventilator associated pneumonia in the ICU: where has it gone? *Curr Opin Pulm Med*, 21:226-231.
[2] Koulenti et al. (2006). Hospital-acquired pneumonia in the 21st century: a review of existing treatment options and their impact on patient care. *Expert Opin Pharmacother*, 7(12):1555-1569.
[3] Kuti et al. (2008). Impact of inappropriate antibiotic therapy on mortality in patients with ventilator-associated pneumonia and blood stream infection: a meta-analysis. *J Crit Care*, 23:91-100.
[4] Melsen et al. (2013). Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomized prevention studies. *Lancet Infect Dis*, 13:665-671.
[5] Sorbello et al. (2010). Registration trials of antibacterial drugs for the treatment of nosocomial pneumonia. *Clin Infect Dis*, 1;51 Suppl 1:S36-41.
[6] Ericson et al. (2020). Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee and the Clinical Trials Transformation Initiative. Hospital-acquired Pneumonia and Ventilator-associated Pneumonia in Children: A Prospective Natural History and Case-Control Study. *Pediatr Infect Dis J*, 39(8):658-664.
[7] Kalil et al. (2016). Management of Adults With Hospitalacquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*, 63(5):e61-e111.

in adults, pediatric patients sometimes require mechanical ventilation for HABP due to acute respiratory failure.

The proposed indication is for the treatment of HABP/VABP in pediatric patients caused by gram-negative pathogens. The most common gram-negative pathogens isolated from patients with HABP or VABP are consistent across geographic regions and age groups and include *P. aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Acinetobacter* spp., and *Enterobacter* spp.[8,9] All of these organisms are associated with antibacterial drug resistance mediated by extended-spectrum β-lactamases and carbapenemases.

2.2. Analysis of Current Treatment Options

Table 1. Currently Available Treatments For Gram-Negative Nosocomial Pneumonia

Generic/Chemical Name	Trade Name	Indication	Approved Age Range for Indication	Comments
Extended-spectrum penicillins				Unlikely to be used alone without tazobactam
Piperacillin	Pipracil	LRTI	Adults only	
Cephalosporins (parenteral 2nd, 3rd and 4th generation)				Use of 2nd and 3rd generation cephalosporins has declined with emergence of multi-drug resistant gram-negative bacilli
Cefotetan	Cefotan	LRTI	Adults only	
Cefoxitin	Mefoxin	LRTI	≥3 months	
Cefuroxime sodium	Zinacef	LRTI	≥3 months	
Cefotaxime	Claforan	LRTI	All ages	
Ceftriaxone	Rocephin	LRTI	≥2 months	
Ceftazidime	Fortaz, Tazicef	LRTI	All ages	
Cefepime	Maxipime	MSP	≥2 months	
Cefiderocol	Fetroja	HABP/VABP	Adults only	
β-lactam/β-lactamase Inhibitor Combinations				
Piperacillin-tazobactam	Zosyn	NP	≥2 months	
Ceftolozane-tazobactam	Zerbaxa	HABP/VABP	Adults only	
Imipenem-cilastatin-relebactam	Recarbrio	HABP/VABP	Adults only	
Carbapenems				
Imipenem-cilastatin	Primaxin	LRTI	All ages	
Meropenem	Merrem	Off label*	Off label*	
Fluoroquinolones				

[8] Sader et al. (2014). Antimicrobial susceptibility of gram-negative organisms isolated from patients hospitalised with pneumonia in US and European hospitals: results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. *Int J Antimicrob Agents*, 43(4):328-334.
[9] Jiang et al. (2019). Antibiotics for hospital-acquired pneumonia in children. *Cochrane Database Syst Rev*, Mar 4;2019(3):CD012239.

Levofloxacin	Levaquin	NP, CAP	Adults only	Risk of tendon rupture, QTc prolongation, CNS effects
Ciprofloxacin	Cipro	LRTI, NP	Adults only	
Moxifloxacin	Avelox	CAP	Adults only	
Monobactams				Used in patients with allergies to penicillins/ cephalosporins
Aztreonam	Azactam	LRTI	≥9 months	
Aminoglycosides				Risk of nephrotoxicity and ototoxicity
Gentamicin sulfate		RTI	All ages	
Amikacin sulfate		SI	All ages	
Tobramycin sulfate		LRTI	All ages	
Polymyxins				Some gram-negatives are intrinsically resistant (e.g., *Proteus* spp. *Providencia* spp. *Serratia* spp., *B. cepacia*), safety risks include nephrotoxicity and rare but serious neurotoxicity
Polymyxin B Sulfate		BA	All ages	
Colistimethate	Coly-mycin M	SI	All ages	

Abbreviations: LRTI Lower respiratory tract infections; NP nosocomial pneumonia; MSP Moderate to Severe Pneumonia; RTI Respiratory tract infections; SI Serious Infections; BA Bacteremia; CAP Community-acquired pneumonia
Note: For empiric therapy, the above drugs may be given in combination with antibacterial drugs with selective activity against gram positive pathogens, such as vancomycin or linezolid for methicillin-resistant *S. aureus*.
*Meropenem is approved for the following indications: complicated skin and skin structure infections (adult and pediatric patients ≥3 months of age); complicated intra-abdominal infections (adults and all pediatric patients); and bacterial meningitis (pediatric patients ≥3 months of age only).

Not all of the above listed antibacterial drugs are approved for use in pediatric patients and the current IDSA HABP/VABP treatment guidelines apply to adult patients only.[10] However, some healthcare systems (e.g., University of North Carolina and University of California-Davis) have established treatment algorithms for pediatric patients with HABP/VABP, which recommend cefepime as the first choice antibacterial drug, with or without concomitant coverage for methicillin-resistant *Staphylococcus aureus* (MRSA). Aztreonam is recommended in patients with severe β-lactam allergies (but is only approved for use in patients ≥9 months) and meropenem is recommended as first-line treatment if there is a history of cephalosporin-resistant infections (for all age groups, but this would be off-label use, as meropenem is not approved for treatment of respiratory tract infections). In general, treatment options for pediatric patients with HABP/VABP are limited, especially in the setting of MDR infections.

[10] Kalil et al. (2016). Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical Infectious* Diseases, 63(5):e61–e111

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

AVYCAZ is a fixed combination antibacterial drug product composed of ceftazidime, a third-generation cephalosporin, and avibactam, a non-β-lactam β- lactamase inhibitor at a ratio of 4:1. AVYCAZ was initially approved in February 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. The data initially submitted in the 505(b)(2) AVYCAZ NDA included PK/PD analyses, in vitro microbiological studies, in vivo animal models of infection, phase 1 clinical pharmacology data, phase 2 clinical data in patients with cIAI and cUTI, and interim phase 3 data, as well as a review of the efficacy of ceftazidime alone. Due to the limited clinical data submitted in the original application, the drug was approved with a statement of limited use. Two subsequent efficacy supplements provided clinical trial data with statistical inference testing to support the removal of the limited use statements. The adult efficacy supplement for cIAI was approved on June 22, 2016 (Supplement 2) and cUTI on January 26, 2017 (Supplement 3). An efficacy supplement to support an indication for treatment of HABP/VABP in adult patients was approved on February 1, 2018 (Supplement 4). Additionally, efficacy supplements 5 and 6 were approved on March 14, 2019 for the indications of cUTI and cIAI in pediatric patients ≥3 months of age.

3.2. Summary of Presubmission/Submission Regulatory Activity

Key regulatory interactions and proceedings relevant for CAZ-AVI development for HABP/VABP:

December 10, 2012: Type C meeting to discuss development plans for treatment of HABP/VABP due to MDR gram-negative bacteria. Advice was sought regarding:

1. An alternative pathway to gain approval for HABP/VABP by performing a relatively small randomized phase 3 study targeting resistant pathogens in HABP/VABP patients.
2. A traditional regulatory pathway for HABP/VABP from a single, statistically powered phase 3 study in HABP/VABP patients.

March 11, 2013: QIDP and Fast Track designations were granted for CAZ-AVI for the indications of cIAI, cUTI, and HABP/VABP.

December 19, 2013: Type B pre-NDA meeting to discuss the format and filing of an NDA for CAZ-AVI based upon nonclinical data, phase 1 data, data from two phase 2 studies, and published ceftazidime data. Additional feedback on seeking an indication for HABP/VABP was provided during the meeting.

June 25, 2014: Initial NDA submitted for the indications of cIAI, cUTI, and aerobic gram-negative infections including HABP/VABP and bacteremia in adults when limited or no alternative treatments are available.

December 5, 2014: Anti-Infective Drugs Advisory Committee meeting — the Sponsor sought approval for the indications of cIAI, cUTI, and aerobic gram-negative infections including HABP/VABP and bacteremia when limited or no alternative treatments are available. The Committee agreed the Sponsor had demonstrated substantial evidence of safety and efficacy of CAZ-AVI for the proposed indications of cIAI and cUTI, but that additional clinical data were needed to support the HABP/VABP indication.

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.

November 3, 2015: Type C meeting to discuss the acceptability of data from Study D4281C00001 to support a HABP/VABP indication in the United States.

May 12, 2017: Type B meeting for proposed sNDA in HABP/VABP.

February 1, 2018: Approval of CAZ-AVI 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* (Supplement 4).

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.

March 14, 2019: Approval of efficacy supplements 5 and 6 to extend the indications of cUTI and cIAI to pediatric patients ≥3 months of age and fulfill PMRs 2862-1 and 2862-2.

May 11, 2021: Type C written response only (WRO) meeting requested to discuss (b) (4) for a pediatric HABP/VABP study. FDA recommended submitting a pediatric assessment in an efficacy supplement for consideration of fulfillment of the PREA PMR.

June 22, 2022: Submission of pediatric efficacy supplement including limited data from a single pediatric PK study (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.

3.3. Foreign Regulatory Actions and Marketing History

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted marketing authorization of CAZ-AVI under the tradename Zavicefta® on June 24, 2016 for the treatment of adults with cIAI, cUTI, HABP (including VABP) and infections

due to aerobic gram-negative organisms where treatment options are limited. EMA has since extended this authorization to include pediatric patients aged ≥3 months with cUTI and cIAI. On September 17, 2020, CHMP adopted an additional extension to include pediatric patients aged ≥3 months for the indications of HABP/VABP and treatment of infections due to gram-negative organisms in patients with limited treatment options.

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

4.1. Office of Scientific Investigations (OSI)

As this sNDA contained PK data from a single study consisting of four patients enrolled across four clinical sites, the Sponsor proposed that a Bioresearch Monitoring (BIMO) package not be included in the sNDA, and the Agency agreed.

4.2. Product Quality

AVYCAZ is a marketed drug. There were no proposed changes to the current chemistry, manufacturing, or controls.

4.3. Clinical Microbiology

Ceftazidime-avibactam is comprised 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 clinical microbiology review dated 1/20/2015).

Study C3591025 was a phase 1 open-label study aimed to characterize the PK of AVYCAZ and assess the safety and tolerability following a single IV infusion in children 3 months to < 18 years with HABP/VABP. A total of 4 patients were enrolled; no clinical microbiology information was provided for these patients.

The Applicant has provided clinical microbiology surveillance studies from patients hospitalized with pneumonia, with Enterobacterales isolates showing ceftazidime-avibactam $MIC_{50/90}$ values of 0.12 and 0.25 mg/L and 2 and 4-8 mg/L against *Pseudomonas aeruginosa* isolates, respectively. Overall, isolates showed similar ceftazidime-avibactam MICs in pediatric patients when compared with isolates obtained from adults (Study Report# CAZ-MC-04 3100-R01-050).

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

5 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology or toxicology data were submitted with the current sNDA. The reader is referred to Dr. Wendelyn Schmidt's and Dr. Armand Balboni's review of the pharmacology/toxicology data in the original NDA submission and to the pharmacology/toxicology review in Section 5 of the NDA Multi-disciplinary Review and Evaluation for NDA 206494 Efficacy Supplements 005 and 006.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology information contained within the current sNDA supports approval of Avycaz® (ceftazidime-avibactam) for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in pediatric patients 3 months of age and older. See Table 2 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 2. Summary of OCP Recommendations and Comments on Key Review Issues

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>Pivotal or supportive evidence of effectiveness</td><td>Pivotal evidence of effectiveness for CAZ-AVI in the treatment of pediatric patients with HABP/VABP is based on extrapolation of effectiveness from adult HABP/VABP patients. This extrapolation of effectiveness at the proposed pediatric dosing regimen is supported by: 1) the predicted similarity in CAZ and AVI exposures in adult and pediatric HABP/VABP patients and 2) achievement of >90% estimated joint probability of CAZ and AVI PK/PD target attainment (PTA) in pediatric HABP/VABP patients following administration of the proposed dosing regimen.</td></tr>
<tr><td>General dosing instructions</td><td>The table below shows the recommended dosing regimen of CAZ-AVI in pediatric patients aged 2 years to <18 years with an estimated glomerular filtration rate (eGFR) greater than 50 mL/min/1.73 m^2, and in pediatric patients aged 3 months to <2 years without renal impairment. All doses are administered as a 2 h infusion with a recommended treatment duration of 7-14 days.
<table>
<tr><th>Age Range</th><th>Dose</th></tr>
<tr><td>2 years to <18 years</td><td>CAZ 50 mg/kg and AVI 12.5 mg/kg to a maximum dose of CAZ 2 g and AVI 0.5 g every 8 h</td></tr>
<tr><td>6 months to <2 years</td><td>CAZ 50 mg/kg and AVI 12.5 mg/kg every 8 h</td></tr>
<tr><td>3 months to <6 months</td><td>CAZ 40 mg/kg and AVI 10 mg/kg every 8 h</td></tr>
</table></td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>The table below shows the recommended dosing regimen of CAZ-AVI in pediatric patients 2 years and older with renal impairment. All doses are administered as a 2 h infusion with a recommended treatment duration of 7-14 days.</td></tr>
</table>

Review Issue	Recommendations and Comments	
	Estimated eGFR (mL/min/1.73m^2)	**Recommended Dosage Regimen**
	31 to 50	CAZ 25 mg/kg and AVI 6.25 mg/kg to a maximum dose of CAZ 1 g and AVI 0.25 g every 8 h
	16 to 30	CAZ 19 mg/kg and AVI 4.75 mg/kg to a maximum dose of CAZ 0.75 g and AVI 0.19 g every 12 h
	6 to 15	CAZ 19 mg/kg and AVI 4.75 mg/kg to a maximum dose of CAZ 0.75 g and AVI 0.19 g every 24 h
	≤5	CAZ 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of CAZ 0.75 g and AVI 0.19 g every 48 h
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.	

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 for pediatric HABP/VABP patients. The clinical pharmacology program is comprised of: 1) a Phase 1, open-label, single-dose PK, safety and tolerability study in hospitalized children 3 months to <18 years of age receiving antibacterial therapy for suspected or confirmed nosocomial pneumonia, which only enrolled a total of 4 patients; 2) CAZ-AVI population PK analyses; and 3) CAZ-AVI joint PTA analysis.

Evidence of effectiveness for the proposed CAZ-AVI dosing regimen in HABP/VABP pediatric patients aged 3 months and older is based on extrapolation of effectiveness from the approved CAZ-AVI dosing regimen for adult HABP/VABP patients. Because HABP/VABP is pathophysiologically similar in adults and children, the efficacious CAZ-AVI exposures in adults are expected to also be effective in children. Population PK analyses demonstrate that the estimated steady-state CAZ-AVI exposures resulting from the proposed dosing regimen in pediatric HABP/VABP patients are similar to the efficacious exposures in adults, thus enabling extrapolation of effectiveness from adults to pediatric patients. Additionally, supportive evidence of effectiveness for the proposed dosing regimen is provided by the results of CAZ-AVI joint probability of PK/PD target attainment analysis (see Section 19.5 for additional details).

Given the similarity in causative pathogens for HABP/VABP and the MIC distributions for isolates obtained from pediatric and adult patients, the achievement of >90% PTA with the proposed pediatric dosage regimen at the established susceptible breakpoint indicates that the same drug activity observed in adult patients may also be expected in pediatric patients. Hence, PTA analysis further supports extrapolation of efficacy from adults to pediatric patients with HABP/VABP (for additional details, see response regarding appropriateness of the proposed dosage regimen below).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the Applicant's proposed dosing regimen (see Table 2) for pediatric HABP/VABP patients 3 months to <18 years of age, which is predicted to produce comparable CAZ-AVI plasma exposures in pediatric HABP/VABP to that in adult HABP/VABP patients at the approved adult dose, is acceptable. Results of CAZ-AVI joint PTA analysis also support the efficacy of the proposed dosing regimen for pediatric patients with HABP/VABP. Additionally, the safety of the proposed dosage regimen (which is the same as the approved regimen in pediatric patients with cUTI and cIAI), is expected to be similar in pediatric HABP/VABP patients relative to those with cUTI and cIAI (see Section 8.2 for additional details).

To extend the evidence of efficacy and safety of CAZ-AVI to the treatment of pediatric patients with HABP/VABP, the Applicant had planned to complete Study C3591025, a Phase 1, open-label, single-dose PK, safety and tolerability study in 32 hospitalized children 3 months to <18 years of age receiving antibacterial therapy for suspected or confirmed nosocomial pneumonia, including VABP. Subjects were to be enrolled across 4 age cohorts (with 8 subjects/cohort) who would each be administered CAZ-AVI as a single IV infusion over a 2-hour period according to subject age, weight and renal function as defined by the recommended dosing regimens summarized in Table 2. However, due to challenges with enrollment imposed by the ongoing COVID-19 pandemic and the EMA's approval of a pediatric HABP/VABP indication (which resulted in withdrawal of European study sites from further participation in the trial), only 4 patients (across 3 age cohorts) successfully completed dosing and PK assessments for this study (see Section 19.4 for additional details). As a result, the Applicant largely relied on existing PK data from pediatric patients with cUTI and cIAI to develop the proposed CAZ-AVI dosing regimen for pediatric patients with HABP/VABP. To assess if PK data from pediatric patients with cUTI and cIAI can predict exposures in pediatric patients with HABP/VABP, we evaluated the approved dosing regimens and CAZ-AVI PK data in adult patients across the approved indications (i.e., cIAI, cUTI and HABP/VABP) and arrived at the following findings:

- The current Avycaz® labeling recommends the same CAZ-AVI dosing regimen for the 3 approved adult indications. A comparison of the Applicant's simulated CAZ-AVI exposures in adults using the approved adult dosing regimen indicates that exposures are generally comparable across all 3 indications (Table 3).

- The numeric differences in these exposures do not amount to a meaningful difference in the estimated joint PTA for CAZ-AVI (as illustrated in Table 3 by the >90% PTA estimates for all 3 indications at the current susceptible breakpoint of 8 µg/mL for relevant pathogens).

Table 3. Predicted $C_{max,ss}$, $AUC_{ss,0-24}$ and Joint PTA Results in 5000 Simulated Adult Patients with cIAI, cUTI, VABP and non-VABP Nosocomial Pneumonia and Normal Renal Function Following Repeated Administration of CAZ-AVI 2.5 g every 8 h as a 2 h IV Infusion

PK Parameter (%CV)	cIAI	cUTI	VABP	Non-VABP
CAZ				
$C_{max,ss}$ (µg/mL)	61.1 (43.6)	73 (47.3)	55.1 (58.7)	75.7 (43.0)
$AUC_{0-24,ss}$ (µg·h/mL)	683 (45.2)	880 (48.9)	719 (63.7)	894 (47.6)
AVI				
$C_{max,ss}$ (µg/mL)	11.5 (83.1)	11.2 (87.0)	10.7 (85.3)	14.7 (92.4)
$AUC_{0-24,ss}$ (µg·h/mL)	121 (72.0)	126 (82.0)	129 (78.9)	164 (93.4)
Joint PTA at an MIC of 8 µg/mL (%)[a]	94.9	95.2	96.1	100

Source: Table 3.1.2–1 of Applicant's Summary of Clinical Pharmacology under NDA 206494/s-04
[a] Results based on PK/PD targets of 50% *f*T>MIC for CAZ and 50% *f*T>CT of 1 µg/mL for AVI

Hence, the adult PK data indicate that the impact of infection type on CAZ-AVI exposure is minimal, and does not warrant indication-specific dosage modifications. Given that the presentation of all 3 infections is similar in adults and pediatrics, it is reasonable to expect similar CAZ-AVI PK in pediatric patients across the 3 indications. Therefore, use of PK data from pediatric patients with cUTI and cIAI to predict exposures in pediatric patients with HABP/VABP is acceptable.

The same dosing regimen approved in pediatric patients with cIAI and cUTI was proposed for the treatment of pediatric patients with HABP/VABP. Previously developed population PK models informed by the existing pediatric cUTI and cIAI PK data were updated with the PK data obtained from the 4 patients with suspected or confirmed nosocomial pneumonia to simulate exposures in pediatric HABP/VABP patients administered the proposed dose (see Section 19.5 for additional details). As shown in Table 4, the predicted $C_{max,ss}$ and $AUC_{ss,0-24}$ values corresponding to the proposed dose are similar or slightly exceed the exposures in adult patients with normal renal function, but fall below the established exposure limits for safety (based on predicted $AUC_{ss,0-24}$ of 1100 µg·h/mL for CAZ and 148 µg·h/mL for AVI in adult patients with mild renal impairment, defined as CrCL of 51-80 mL/min/1.73m^2).

Table 4. Predicted CAZ and AVI $C_{max,ss}$, $AUC_{0-24,ss}$, and Joint PTA in 1000 Simulated Pediatric Patients With HABP/VABP and Normal Renal Function by Age Group

Age Group	Dose[a] (CAZ/AVI)	HABP/VABP				
		Ceftazidime Exposure[b]		Avibactam Exposure[b]		Joint PTA at an MIC of 8 mg/L (%)[c]
		$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	$C_{max,ss}$ (mg/L)	$AUC_{ss,0-24}$ (mg•h/L)	
12 to < 18 yrs	50/12.5 mg/kg q8h	70.7 (25.5)	740 (31.9)	13.1 (64.3)	118 (50.7)	99.7
6 to < 12 yrs	50/12.5 mg/kg q8h	81.8 (20.6)	798 (29.8)	15.8 (40.3)	136 (36.8)	96.9
2 to < 6 yrs	50/12.5 mg/kg q8h	77.2 (21.5)	690 (28.7)	14.5 (45.7)	116 (40.8)	91.5
1 to < 2 yrs	50/12.5 mg/kg q8h	75.9 (18.9)	684 (27.7)	14.9 (45.3)	122 (40.3)	94.1
6 to < 12 mths	50/12.5 mg/kg q8h	80.1 (19)	755 (28)	15.4 (45.6)	129 (40.4)	98.1
3 to < 6 mths	40/10 mg/kg q8h	70.9 (18.9)	727 (27.8)	13.3 (46)	117 (40.3)	99.5
Adults	2000/500 mg q8h	65.8 (29.7)	713 (39)	10.6 (72.4)	105 (66)	96.2

[a] Following repeated doses as a 2 h IV infusion with a maximum dose of 2000 mg CAZ and 500 mg AVI
[b] Values are reported as geometric mean (geometric CV%)
[c] PK/PD target of 50% *f*T>MIC for CAZ and 50% *f*T>CT of 1 µg/mL for AVI
Source: Table 3.2.2-1 of Applicant's Summary of Clinical Pharmacology for NDA 206494/s-11

The Applicant also conducted joint PTA analysis using the proposed dosing regimen for pediatric patients with HABP/VABP (see Section 19.5 for additional details). The same PK/PD targets used in adults were selected for PTA analyses in pediatric patients with HABP/VABP (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 HABP/VABP and their MIC distributions are similar for adults and children (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 (Table 4) indicate that at the proposed CAZ-AVI dosage, PTA in pediatric HABP/VABP patients is predicted to exceed 90% at the current breakpoint of 8 µg/mL for susceptible pathogens.

Taken altogether, the predicted comparability to adult exposures and >90% PTA for CAZ-AVI in pediatric patients with HABP/VABP indicate that the Applicant's proposed dosing regimen (see Table 2) for pediatric HABP/VABP patients 3 months to <18 years of age is acceptable.

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

Yes, an alternative dosing regimen is required in pediatric patients with renal impairment. Because both CAZ and AVI are eliminated exclusively by renal excretion, the effect of renal impairment on drug exposure was previously evaluated in adult subjects with renal impairment as described in the approved labeling. The FDA and Applicant previously agreed on dosage adjustments for use in pediatric patients with cIAI and cUTI aged ≥2 years with eGFR ≤50 mL/min/1.73m^2 (as summarized in Table 2). Under this current supplement, the Applicant used the updated population PK models to confirm the appropriateness of the recommended dosage adjustments for renally impaired pediatric patients (see Section 19.5 for additional details). For patients aged <2 years, there remains 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 review was based on one pediatric single dose PK study in patients with HABP/VABP (Study D4280C00028 [C3591025]), as well as safety data from two prior pediatric studies in patients with cIAI (Study D4280C00015) and cUTI (Study D4280C00016). Adult HABP/VABP study safety data (Study D4281C00001) were also reviewed.

Table 5. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
D4281C00001	NCT01808092	Randomized, double-blinded, actively controlled, noninferiority study for **HABP/VABP** in adults	CAZ-AVI (2.5g q8h administered IV over 2 hours) Or Meropenem (1g q8h administered IV over 30 minutes)	Primary: 28 Day all-cause mortality	Treatment: 7 to 14 days Final protocol follow-up on study Day 28	870 subjects (436 in the CAZ-AVI group and 434 in the meropenem group)	Hospitalized patients with HABP/VABP aged 18 to 90	146 study sites 24 countries
Studies to Support Safety								
C3591025	NCT04040621	Open label, single dose, PK, safety and tolerability study in pediatric patients aged 3 months to <18 years hospitalized for **HABP/VABP**	<u>Cohort 1</u>: 12y to <18y and <u>Cohort 2</u>: 6y to <12y • ≥40kg: 2g CAZ / 500mg AVI q8h • <40kg: 50mg/kg CAZ / 12.5mg/kg AVI q8h <u>Cohort 3</u>: 2y to <6y and <u>Cohort 4A</u>: 1y to <2y • 50mg/kg CAZ / 12.5mg/kg AVI q8h <u>Cohort 4B</u>: 3m to <1y • 6m to <1y: 50mg/kg	Primary: PK, safety and tolerability	Treatment: Single-dose of CAZ-AVI	4 subjects received CAZ-AVI (planned for 32 subjects)	Hospitalized patients receiving systemic antibacterial drug therapy for HABP/VABP aged 3 months to <18 years	Planned for 43 study sites and 14 countries
D4280C00015	NCT02475733	Randomized, single-blind safety, tolerability, and descriptive			Treatment: Minimum 72h IV dosing, optional switch to	83 subjects (61 in CAZ-AVI group and 22 in the	Hospitalized patients with cIAI aged 3 months to <18 years	64 study sites 12 countries

		efficacy study in pediatric patients aged 3 months to <18 years with **cIAI**	CAZ / 12.5mg/kg AVI q8h • 3m to <6m: 40mg/kg CAZ / 10mg/kg AVI q8h Doses halved for subjects with CrCL >30 to ≤50 mL/min		oral therapy on Days 4 to 15	meropenem group)		
D4280C00016	NCT02497781	Randomized, single-blind safety, tolerability, and descriptive efficacy study in pediatric patients aged 3 months to <18 years with **cUTI**				95 subjects (67 in CAZ-AVI group and 28 in the cefepime group)	Hospitalized patients with cUTI aged 3 months to <18 years	61 study sites 10 countries

AVI = avibactam; CAZ = ceftazidime; CAZ-AVI = ceftazidime-avibactam; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infections; IV = intravenous; PK = pharmacokinetic(s); q8h = every 8 hours; R = randomized.
Source: Module 5.2

7.2. Review Strategy

Study C3591025 was designed with a relatively small sample size and primary objective of evaluating PK of CAZ-AVI in pediatric patients with HABP/VABP. As only four subjects were enrolled in this study, additional safety data from the pediatric cIAI/cUTI studies and adult HABP/VABP studies were reviewed.

No efficacy data were analyzed in pediatric Study C3591025, as it was a single-dose study. Based on similarities of PK, HABP/VABP pathophysiology, and microbiology in adults and children, efficacy data from Study D4281C00001 (a phase 3 pivotal study demonstrating the safety and efficacy of CAZ-AVI in the treatment of adult patients with HABP/VABP) were used to extrapolate evidentiary support for the proposed indication of treatment of HABP/VABP in pediatric patients aged ≥ 3 months to 18 years.

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 will not be applicable to this review. No sections of the template will be omitted, but instead, irrelevant sections will be noted where appropriate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Adult HABP/VABP Study D4281C00001

Trial Design

Efficacy of CAZ-AVI in pediatric patients with HABP/VABP was extrapolated from the adult HABP/VABP study (D4281C00001), as the pathophysiology of HABP/VABP and the responsible pathogens are similar in both populations.

Study D4281C00001 was a randomized, multicenter, double-blind, double-dummy, parallel-group comparative clinical trial to determine the efficacy, safety, and tolerability of CAZ-AVI versus meropenem for the treatment of HABP and VABP in adult patients.

The primary objective was to compare CAZ-AVI with meropenem with respect to 28-day all-cause mortality in the intent-to-treat (ITT) population using a justified, pre-specified 10% noninferiority margin. The key secondary objectives compared CAZ-AVI with meropenem with respect to 28-day all-cause mortality in the microbiological intent-to-treat (micro-ITT) population and the clinical response at the test of cure (TOC) visit in the ITT population.

Study Endpoints

The primary endpoint was all-cause mortality at Day 28 (+ 4 days) from randomization in the ITT population, which included all randomized patients receiving at least one dose of study drug. Endpoints were assessed for the ITT population and for the micro-ITT population, which included all patients with positive culture results indicating the presence of at least one gram-negative pathogen. Clinical cure at the TOC visit (21-25 days from randomization) was also evaluated. Clinical cure was defined as resolution or significant improvement in signs and symptoms associated with pneumonia and cessation of antibacterial treatment for HABP/VABP.

8.1.2. Study Results

Efficacy Results

CAZ-AVI was found to be non-inferior to meropenem in the treatment of adult patients with HABP/VABP with respect to 28-day all-cause mortality in the ITT population (CAZ-AVI mortality 9.6%, meropenem 8.3% [difference 1.48%; 95% CI: - 2.38 to 5.33]). The secondary endpoint of clinical cure supported the finding of non-inferiority. The favorable clinical response at TOC in the ITT population was 67.2% and 69.1%, in the CAZ-AVI and meropenem groups, respectively (difference -1.9%; 95% CI: - 8.10 to 4.27).

8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review is based on a phase 1 multicenter, multinational, open-label single-dose PK study evaluating the safety and tolerability of CAZ-AVI in pediatric patients aged ≥3 months to <18 years who were hospitalized for HABP/VABP (Study C3591025). Safety assessments occurred through the late follow-up (LFU) visit between Study Days 28 and 35. Only four subjects completed the study, therefore two additional phase 2 single-blind, randomized, multicenter active-controlled studies of pediatric patients aged ≥3 months to <18 years were considered in the safety review: (1) Study D4280C00015 compared CAZ-AVI + metronidazole to meropenem for treatment of cIAI; and (2) Study D4280C00016 compared CAZ-AVI to cefepime for treatment of cUTI. These prior pediatric studies will be discussed further in the Section 8.2.8.

8.2.2. Review of the Safety Database (Study C3591025)

Overall Exposure and Patient Demographics

Patients were eligible for the study if they were aged ≥3 months to <18 years, were hospitalized and receiving systemic antibiotic therapy for suspected or confirmed HABP or VABP. Planned study cohorts are listed in Table 6 below.

Table 6. Planned Study Cohorts (Study C3591025)

Cohort	Age Range	Number of Subjects
1	≥12 years to <18 years	N=8
2	≥6 years to <12 years	N=8
3	≥2 years to <6 years	N=8
4A	≥1 year to <2 years	N=4
4B	≥3 months to <1 year	N=4

Source: Module 5.3.5.2

A total of 32 patients were initially planned for enrollment in this study. However, due to recruitment issues, only four total patients were enrolled (Table 7). Each patient was exposed to a single dose of CAZ-AVI and all four patients completed the study. The median age was 3.4 years (ranging from 11.6 months to 9.4 years).

Table 7. Demographic and Baseline Characteristics (Study C3591025)

Parameter	CAZ-AVI (N=4)
Sex	
F	1 (25.0)
M	3 (75.0)

Parameter	CAZ-AVI (N=4)
Race	
Asian	4 (100.0)
Age (years)	
Mean (SD)	4.3 (3.79)
Median (Min, Max)	3.4 (0.97, 9.36)

Source: OCS Analysis Studio

Adequacy of the safety database

The safety database for Study C3591025 alone was limited, therefore two additional pediatric studies were included in the safety assessment (D4280C00015 [cIAI] and D4280C00016 [cUTI]). Collectively, this combined database was adequate in terms of size and population of interest (pediatric patients aged 3 months to <18 years). Safety evaluations included vital signs, routine physical examinations, and laboratory tests. Patients were monitored for adverse events including cephalosporin class effects. Adverse events of special interest (liver disorder, diarrhea, hypersensitivity/anaphylaxis, hematological disorder, and renal disorder) were identified and recorded.

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 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 24.1), 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

A serious adverse event (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 days after the last administration of the investigational product. All serious and nonserious AEs were recorded in the CRF and SAEs were reported to the Applicant within 24h of onset. Causality assessments were performed by the investigator for all AEs.

Routine Clinical Tests

Routine clinical tests done at baseline and at specified time points included complete blood count with differential, chemistry panel, creatinine clearance (CrCl) calculation (using bedside Schwartz formula), creatine kinase, lactate dehydrogenase, urine or serum pregnancy test in female patients of child-bearing age, and urinalysis. Chest X-ray or other imaging performed at baseline and as needed as part of subjects' medical care. Complete physical exam including height, weight and body mass index measurements was done at screening and at subsequent visits. One set of vital signs including pulse, blood pressure, body temperature, respiratory rate, and oxygen saturation were recorded at each visit.

8.2.4. Safety Results

Overview of Adverse Events

Table 8 displays an overview of AEs from Study C3591025. There were 16 total AEs reported among the four patients who received CAZ-AVI. There were no AEs with outcomes leading to death. Nearly all AEs were reported as mild, but there was one SAE reported in Cohort 4B that was also of severe intensity. Two of the reported AEs (rash and pyrexia) were considered potentially related to the study drug. Of note, the clinical study report (CSR) listed only 15 AEs. However, the AE dataset included 16 total AEs, as one patient ((b) (6)) reported two separate episodes of pyrexia on different study days (i.e., Day 2 and Day 19), but only the Day 2 event was listed in the CSR and was considered potentially related to the study drug.

Table 8. Overview of Treatment-Emergent Adverse Events up to LFU (Study C3591025)

Adverse Event Category	Cohort 2 (N=1)	Cohort 3 (N=1)	Cohort 4A (N=1)	Cohort 4B (N=1)	All Cohorts (N=4)
Any AE	0	1	1	1	3 (75%)
Any AE with outcome leading to death	0	0	0	0	0
Any SAE	0	0	0	1	1 (25%)
Any AE with severe intensity	0	0	0	1	1 (25%)
Any AE of special interest	0	0	1	0	1 (25%)
Any AE related to study drug	0	0	1	1	2 (50%)

Cohort 1: ≥12 years to <18 years of age; Cohort 2: ≥6 years to <12 years; Cohort 3: ≥2 years to <6 years; Cohort 4A: ≥1 year to <2 years; Cohort 4B: ≥3 months to <12 months); AE: adverse event; SAE: serious adverse event; N: number of participants in the specified cohort

Source: Reviewer table, Module 5.3.5.2

Deaths

No deaths were reported in Study C3591025.

Serious Adverse Events

One SAE was reported in Cohort 4B, which in the opinion of the investigator and reviewer was unrelated to the study drug. The case narrative is described below.

Subject (b) (6) was an 11-month-old male from Taiwan with a past medical history of congenital myotonic dystrophy, arthrogryposis resulting from suspected neuromuscular diseases, multiple unspecified congenital anomalies, and ventilator-dependence at baseline, who was diagnosed with nosocomial pneumonia and admitted to the pediatric intensive care unit (PICU). The patient was enrolled in the study and received a single dose of CAZ-AVI on Study Day 1. The patient had already been started on piperacillin-tazobactam on Study Day -2 for treatment of concurrent UTI, which was switched to cefuroxime from Day 11 through Day 22. The patient's respiratory status initially improved and he was discharged from PICU on Study Day 15. However, on Day 18 he experienced an SAE of acute respiratory distress syndrome (ARDS) and was transferred back to the PICU for increased ventilator support. Other reported AEs for this patient occurred around this time, including pyrexia, elevated brain natriuretic peptide (BNP), hypoglycemia, and metabolic alkalosis—all likely related to the underlying condition. In the opinion of the investigator and reviewer, the SAE of ARDS was unrelated to the study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

No dropouts or discontinuations were reported.

Significant Adverse Events

Known cephalosporin class effects including liver disorders, hypersensitivity reactions, hematological disorders, and renal disorders were deemed AEs of special interest (AESI). Three events were AESIs—elevated ALT and AST and rash. These occurred in a single patient. The AE of rash occurred around the same time as the CAZ-AVI infusion and was assessed as mild and potentially related to the study drug. The patient received the full dose of CAZ-AVI and the rash resolved within 48 hours.

With regard to the elevated transaminases, ALT/AST levels were already borderline high/elevated at screening (ALT: 43.4 U/L at screening to 80.9 U/L at follow-up; AST: 56.4 U/L at screening to 91.2 U/L at follow-up). Although this patient's transaminitis was unlikely to be related to the study drug, increased ALT and AST are listed as possible AEs in the labeling for ceftazidime and AVYCAZ.

Treatment Emergent Adverse Events and Adverse Reactions

In total, 16 TEAEs were reported by three of the four patients enrolled in the study (Table 9). All reported AEs were mild except one SAE (ARDS) of severe intensity that was not treatment-related. Two AEs were considered related to the study drug treatment in the opinion of the investigator. These were rash (Subject (b) (6), Cohort 4A) and pyrexia (Subject (b) (6), Cohort 4B). There were no new or unexpected safety signals reported in this study that warrant labeling changes.

Table 9. Incidence of Treatment-Emergent Adverse Events by Preferred Term (PT) up to LFU (Study C3591025)

TEAEs by Preferred Term	Cohort 2 N=1	Cohort 3 N=1	Cohort 4A N=1	Cohort 4B N=1	All Cohorts N=4 (% of patients)
Any TEAE	0	1	1	1	3 (75%)
Pyrexia	0	1	0	1	2 (50%)
Acute respiratory distress syndrome	0	0	0	1	1 (25%)
Alanine aminotransferase increased	0	0	1	0	1 (25%)
Aspartate aminotransferase increased	0	0	1	0	1 (25%)
Brain natriuretic peptide increased	0	0	0	1	1 (25%)
Dermatitis diaper	0	0	0	1	1 (25%)
Headache	0	1	0	0	1 (25%)
Hernia	0	0	0	1	1 (25%)
Hypoglycemia	0	0	0	1	1 (25%)
Metabolic alkalosis	0	0	0	1	1 (25%)
Protein urine present	0	0	1	0	1 (25%)
Rash	0	0	1	0	1 (25%)
Tonsillar hypertrophy	0	1	0	0	1 (25%)
Urethral disorder	0	1	0	0	1 (25%)

Source: OCS Analysis Studio

Reviewer comment:

With regard to the likely treatment-related AEs, the rash reported in Cohort 4A may have been related to the study drug based on temporality and known risk of hypersensitivity reactions with this drug class (included in the ceftazidime labeling). However, the severity was reported as mild and there were no reports of anaphylaxis or other symptoms consistent with a hypersensitivity reaction.

The initial episode of pyrexia reported in Cohort 4B could also have plausibly been related to the study drug, as it occurred on Study Day 2; however, this patient was also very ill and being treated for concurrent nosocomial pneumonia and UTI, so the reported fever may have been related to the underlying infections. Of note, a second episode of pyrexia was reported in the same patient on Study Day 19, around the time he developed ARDS, which was not mentioned in the CSR or included in the Sponsor's

analyses, but was included in the AE dataset. Per the investigator, this episode of pyrexia may have been related to concomitant drug treatment or underlying infection and reviewer agrees it was likely unrelated to the study drug.

Laboratory Findings

There were no significant trends in laboratory values aside from those previously discussed.

Vital Signs

No clinically significant changes in vital sign parameters were reported.

Electrocardiograms (ECGs)

ECGs were not performed as part of the safety assessment for this study. Prior studies showed no clinically significant changes in ECG/QT parameters.

Immunogenicity

There are no studies evaluating the immunogenicity of 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

Analysis by demographic subgroup was not performed due to the small sample size.

8.2.8. Specific Safety Studies/Clinical Trials

As stated previously, the safety database for Study C3591025 alone was limited, therefore two additional pediatric studies were included in the safety assessment (D4280C00015 [cIAI] and D4280C00016 [cUTI]). Of note, AESIs for these studies included diarrhea, liver disorders, hypersensitivity reactions, hematological disorders, and renal disorders. A summary of safety data from these studies is included below.

cIAI

In the cIAI study, the most common AEs were vomiting and infusion site reactions, occurring in 14.8% (9/61) and 6.6% (4/61) of CAZ-AVI-treated patients, respectively. There were no deaths, dose modifications or discontinuations due to AEs. There were five SAEs reported by five patients in the CAZ-AVI group—ileus, intestinal obstruction, large intestinal perforation, renal colic, and vomiting. Per the original clinical review for this study, renal colic (nephrolithiasis) was the only AE already included in the AVYCAZ labeling, occurring in <1% of adult patients in phase 3 trials. The other SAEs were considered unlikely to be related to the study drug, but the role of CAZ-AVI could not be excluded.

There were four patients with AESIs in the CAZ-AVI group, one with diarrhea and three with hypersensitivity reactions including cough, pruritus, and rash. No patients were reported to have *C. difficile* infection. Per the clinical reviewer of the pediatric cIAI efficacy supplement, cough, rash, and pruritus could have been hypersensitivity reactions related to the study drug, but there was no evidence of anaphylaxis. One patient in the CAZ-AVI group had a negative Coombs test at baseline which was later positive. This is a known effect of cephalosporins, but there were no reports of symptomatic hemolytic anemia associated with Coombs seroconversion. Of note, there were no reports of liver or renal disorders.

cUTI

In the cUTI study, the most common AEs in the CAZ-AVI group were diarrhea (7.5%) and UTI (7.5%). Diarrhea is an expected adverse reaction for cephalosporins, but UTIs were not seen as adverse reaction by the clinical reviewer of the pediatric cUTI efficacy supplement, rather as possible treatment failures or emergent infections. There were eight SAEs reported in the CAZ-AVI group. Of these, five were reports of UTI/pyelonephritis related to the underlying infection, one patient developed nephrolithiasis (but had a prior history of kidney stones), one patient developed a severe viral infection on Study Day 35 (32 days after last dose of study drug), and one patient reported neurological symptoms resulting in CAZ-AVI discontinuation (described below). All of these were assessed as unlikely to be related to the study drug.

There were no deaths or dose adjustments, but three AVYCAZ patients discontinued the study drug due to AEs. One patient reported an SAE of nonspecific neurological symptoms (tingling, numbness, weakness) which resolved without intervention and may have been preexisting. Another patient reported tachycardia following study drug infusion, which also resolved spontaneously (patient was tachycardic at baseline). These events were deemed unlikely to be related to the study drug per the investigator and clinical reviewer of the pediatric cUTI efficacy supplement. A third patient developed dizziness, nausea, and vomiting on Study Day 2, which were deemed potentially related to the study drug and CAZ-AVI was discontinued. Dizziness, nausea and vomiting are known to be common adverse effects of CAZ-AVI and are already reported in the labeling.

There were 10 patients with AESIs in the CAZ-AVI group. No patients were reported to have hematological disorders or renal disorders. There were 2 patients from each treatment group

who initially had a negative Coombs test that later turned positive, but they did not have symptomatic hemolytic anemia. One patient had mildly elevated GGT which may have been related and five patients reported diarrhea, but there were no cases of *C. difficile*. Two patients reported cough and three reported rash, which may have been hypersensitivity reactions related to the CAZ-AVI, but no evidence of anaphylaxis.

Reviewer comment:

No unexpected safety signals were reported in either of the prior pediatric studies and AEs were generally similar across all clinical trials. The most common AEs such as diarrhea and hypersensitivity reactions are included in the labeling.

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

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Division of Pharmacovigilance reviewed all serious FDA Adverse Event Reporting System (FAERS) reports with CAZ-AVI in the pediatric population (ages 0 to <18 years) received from February 25, 2015 through January 20, 2022. Of the 37 cases evaluated, 13 were unique reports resulting in death, but the relationship between death and CAZ-AVI use was unassessable in

most cases and was more likely related to the underlying infection or comorbid conditions. No serious unlabeled adverse events associated with CAZ-AVI were identified.

A 120-day safety update was submitted by the Applicant, covering the period from February 24, 2022 to June 22, 2022. One clinical study was ongoing during this time (C3591024, neonatal sepsis study). One 15-day safety report was submitted for this study from a 14-day-old patient who developed neonatal neutropenia. The preferred term 'neutropenia neonatal' was considered unlabeled; however, 'neutropenia' is included in the AVYCAZ labeling. With regard to postmarketing data, six case reports were received—five serious and one nonserious. Three of the serious AEs resulted in death, but did not appear to be related to the study drug. A PubMed search 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

No potential safety concerns are expected beyond the current prescribing information for AVYCAZ.

8.2.11. Integrated Assessment of Safety

A total of 132 pediatric patients were exposed to CAZ-AVI across the three pediatric studies conducted in patients aged 3 months to <18 years with cUTI, cIAI, or HABP/VABP. There were no deaths and no new safety signals were identified in Study C3591025, which enrolled 4 pediatric patients with HABP/VABP. In this study, there were 16 total ARs reported, of which rash and pyrexia were assessed as potentially related to the study drug and are known class effects of cephalosporins. Mild elevations in hepatic enzymes were reported in a single patient, which are also included in the AVYCAZ labeling. No other concerning trends in laboratory values were observed in this study.

With regard to the prior pediatric studies for cUTI and cIAI, the most common AEs were diarrhea in the cUTI study and vomiting and infusion site reactions in the cIAI study; all are also known cephalosporin class effects.

There were no cases of anaphylaxis or *C. difficile*-associated diarrhea in any of the pediatric studies. There are no new concerns based on post-marketing reports. Overall, the safety profile of CAZ-AVI in pediatric patients with HABP/VABP appears similar to the safety profile in pediatric patients with cUTI and cIAI.

8.3. Statistical Issues

No statistical issues were identified, as Study C3591025 was a single-dose study and efficacy data were not collected.

8.4. Conclusions and Recommendations

Study C3591025 was a phase 1 open-label study to characterize the PK of AVYCAZ and assess the safety and tolerability following a single IV infusion in pediatric patients ≥3 months of age with HABP/VABP. As only four subjects were enrolled in pediatric Study C3591025, additional safety data from the pediatric cIAI/cUTI studies and adult HABP/VABP studies were also reviewed. The safety profile of CAZ-AVI in Study C3591025 was similar to that in pediatric patients with cUTI and cIAI as well as adults with HABP/VABP. No unlabeled safety signals were reported in this study and there were no deaths.

Substantial evidence of effectiveness to support the approval of AVYCAZ for treatment of HABP/VABP caused by susceptible gram-negative microorganisms in pediatric patients aged ≥3 months to <18 years was extrapolated from the adult HABP/VABP study (Study D4281C00001), as the pathophysiology of HABP/VABP and the responsible pathogens are similar in both populations.

Overall, CAZ-AVI has a favorable safety and efficacy profile for the treatment of HABP/VABP in pediatric patients aged 3 months to <18 years. The risks associated with CAZ-AVI use in the pediatric population can be adequately addressed through the product labeling and routine postmarketing surveillance. The review team recommends approval of this application and fulfillment of PMR 2862-6.

9 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting convened for this sNDA.

10 Pediatrics

CAZ-AVI has previously been approved for use in pediatric patients aged 3 months to <18 years with cIAI and cUTI. This efficacy supplement contains a pediatric assessment for patients aged 3 months to <18 years with HABP/VABP.

An additional PMR (PMR 2862-3) was issued to conduct a trial to evaluate the PK, safety and tolerability of CAZ-AVI in patients from birth to <3 months with late-onset sepsis. There is an ongoing pediatric Study C3591024 titled, "A Phase 2a, 2-part, open-label, non-randomized, multicenter, single and multiple dose trial 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 design is included in Table 10 below.

In September 2021, the Applicant requested a one year deferral extension for completion of Study C3591024 to December 2022. This request was based on various issues faced by the Applicant with conduct of the study, including issues with site identification, clinical trial agreement withdrawals and rejections, recruitment challenges, and the COVID-19 pandemic. The deferral extension was granted by FDA on November 4, 2021.

At the time of this review, the Applicant had completed enrollment in all cohorts except Cohort 2B (full term neonates from birth to ≤ 28 days receiving 20/5 mg/kg CAZ-AVI infusion over a 2-hour period every 8 hours), in which 6 out of 8 planned participants have been enrolled, 5 of whom are evaluable for safety and 4 of whom are evaluable for PK. On August 29, 2022, the Applicant submitted a Type C meeting request to obtain the Division's input on whether the clinical/PK data package anticipated to be available by the study C3591024 completion milestone of December 2022 will be sufficient to fulfill PMR 2862-3 and to support the filing of an sNDA seeking approval of AVYCAZ administration in pediatric patients aged from birth to <3 months across indications. The Division agreed that the data package should be sufficient to support the filing of this sNDA, but fulfillment of PMR 2862-3 will be a review issue.

Table 10. Design of Ongoing Pediatric Clinical Study C3591024

Study	Age and Cohorts	Design
C3591024 [PMR 2862-3]	**Neonatal sepsis Part A**: • Cohort 1A: Full-term infants age ≥28 days to <3 months	**Part A**: Single dose PK **Part B**: Multiple-dose PK

	• Cohort 2A: Full-term neonates gestational age of ≥37 weeks to <28 days • Cohort 3A: Pre-term neonates with gestational age of at least 26 to 37 weeks **Part B**: Cohorts as for Part A	Planned number of patients: **Part A**: at least 24 patients, 8 per cohort (all to receive single-dose CAZ-AVI) **Part B**: at least 12 patients, (all to receive multiple-dose CAZ-AVI)

11 Labeling Recommendations

11.1. Prescription Drug Labeling

This Prescribing Information (PI) review includes a high-level summary of the major changes made to the submitted PI by the Applicant on June 22, 2022. Several sections of the PI were revised during this review cycle. Table 11 below summarizes key changes and the rationale for these changes as reviewer's comments.

Table 11. Summary of Key Changes to the Prescribing Information

Section and /or Subsection of the PI	Applicant's proposed text	Revised Text and Rationale for Changes
HIGHLIGHTS OF PRESCRIBING INFORMATION		
ADVERSE REACTIONS	Headings in this subsection included the following: • Adult (b) (4) Patients • Pediatric (b) (4) Patients	Headings in this subsection edited to: • Adult Patients • Pediatric Patients
Reviewer comment: The subheadings in the adverse reactions (AR) section of the Highlights were revised to state "Adult Patients" and "Pediatric Patients" since the adult ARs are listed by indication in the paragraph itself and the pediatric ARs are the same across indications.		
FULL PRECRIBING INFORMATION		
Section 1: **INDICATIONS AND USAGE**	'Adult and pediatric patients 3 months or older' (1.1, 1.2, 1.3)	'Adult and pediatric patients aged 3 months and older' (1.1, 1.2, 1.3)
Reviewer comment: Description of the specific age group was changed throughout the PI to be more consistent with the labeling recommendations in the 'Pediatric Information Incorporated Into Human Prescription Drug and Biolreviewer cogical Product Labeling Guidance for Industry.'		
Section 6: ADVERSE REACTIONS Subsection 6.1 Clinical Trials Experience	Clinical Trials Experience in Pediatric Patients Added the following paragraph at end of the subsection:	Clinical Trials Experience in Pediatric Patients Deleted paragraph proposed by the Applicant and added the following

	(b) (4)	pediatric HABP/VABP study data to first paragraph: 'An open-label single-dose pharmacokinetic (PK) and safety trial was conducted in pediatric patients with HABP/VABP and enrolled four patients aged 11.6 months to 9.4 years *[see Clinical Pharmacology 12.3]'* Added HABP/VABP indication to the safety profile statement: 'The safety profile of AVYCAZ in pediatric patients was similar to adults with cIAI, and cUTI, and HABP/VABP treated with AVYCAZ.'
Reviewer comment: Recommended deleting the last paragraph in the section given that this information is generally summarized in Section 8.4 Pediatric Use. Additionally, recommended removal of the sentence (b) (4) *, as safety was not directly extrapolated using these models. As the safety profile was similar across pediatric studies, this statement was updated to include all three indications (cIAI, cUTI, HABP/VABP). Refer to section 8.2.11 for additional details.*		
Section 8: USE IN SPECIFIC POPULATIONS **Subsection 8.4 Pediatric Use**	The following paragraph was added to this subsection: (b) (4) Last sentence of subsection states: 'There is insufficient information to recommend dosage adjustment for pediatric patients younger than 2 years of age with (b) (4)	Deleted paragraph proposed by the Applicant and added the HABP/VABP indication to the initial paragraph describing the data used to establish Avycaz safety and effectiveness in this pediatric population. Also recommended removing the last sentence in this subsection, as pediatric dosing in the setting of renal impairment is addressed in subsections 2.3, 8.6, and 12.3.

	renal impairment *[see Dosage and Administration (2.3)]*.'	
Reviewer comment: Included the HABP/VABP indication within the first two paragraphs of this subsection, as the pediatric safety profile was similar across indications. Additionally, statements regarding pediatric dosing in the setting of renal impairment are included in multiple other subsections.		
Section 12: CLINICAL PHARMACOLOGY Subsection 12.3 PHARMACOKINETICS	The Applicant revised the *Pediatric Patients* subheading to extend the existing language to pediatric HABP/VABP patients, elaborate on the data sources used to inform the population PK model and dosage selection for the 3 indications: 'Population pharmacokinetic analyses and target attainment simulations were conducted for recommendation of AVYCAZ dosing in pediatric patients with cIAI, cUTI and HABP/VABP. (b) (4)	The second sentence of the Applicant's proposed text, which details the types of studies which informed the population PK model, is not needed since it does not serve to subsequently highlight differences in PK in pediatrics across the 3 indications. Instead, existing language in this subsection of the current labeling which reads, "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 3 months to less than 2 years without renal impairment result in systemic exposures similar to that in adult patients given AVYCAZ 2.5 grams. Population PK modeling, including the assumption of proportional effects of renal impairment in adults and pediatric patients, also predicted that the recommended dose adjustments for patients aged 2 years and older with eGFR less than 50 mL/min/1.73 m^2 result in systemic exposure similar to that in adult patients" adequately summarizes PK data from these patient populations. Therefore, the second sentence was deleted. Also deleted the last sentence of the Applicant's proposed text (b) (4) because this has already been addressed in subsection 8.4.

		Additionally, recommended a clarifying edit to the approved labeling language to specify that the recommended dosing regimens in pediatric patients (which are informed by modeling and simulation) are predicted to result in systemic exposures similar to that in adult patients given the approved dose.
Reviewer comment: The recommended edits are intended to streamline the contents of this subsection in accordance with the FDA's Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products-Content and Format, Guidance for Industry. The guidance encourages brevity in the description of studies and their results; because details surrounding (b) (4) *are not informative to clinical use, these descriptions were removed. Refer to Sections 6 and 15.5 for additional details.*		

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. No new PMRs will be issued with approval of this sNDA.

14 Division Director (Clinical) Comments

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

15 Appendices

15.1. References

References are included as footnotes on the pages where they are cited.

15.2. Financial Disclosure

The Applicant submitted a certification of financial interest (form 3454) in accordance with 21 CFR part 54. There were no financial arrangements disclosed between principal investigators and the Applicant for the trial.

Covered Clinical Study (Name and/or Number): C3951025

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 43		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the	Yes ☐	No ☐ (Request explanation

reason:		from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

Not applicable.

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

Study C3591025

Study C3591025 was a Phase 1, open-label, single-dose study to assess the PK, safety and tolerability of CAZ-AVI in children 3 months to <18 years of age who are hospitalized and receiving systemic antibacterial drug therapy for suspected or confirmed nosocomial pneumonia, including ventilator-associated pneumonia. The study was intended to enroll 32 participants across 4 age cohorts to provide PK data for extrapolation of efficacy for HABP/VABP from adults to pediatrics. The 4 age cohorts were defined as follows:

- Cohort 1: ≥ 12 years to < 18 years
- Cohort 2: ≥ 6 years to < 12 years
- Cohort 3: ≥ 2 years to < 6 years
- Cohort 4A: ≥ 1 year to < 2 years; Cohort 4B: ≥ 3 months to < 12 months

Patients were administered CAZ-AVI as a single IV infusion over a 2-hour period with CAZ-AVI doses as shown in Table 2.

However, recruitment challenges that were worsened by the COVID-19 pandemic and EMA approval of a pediatric HABP/VABP indication for AVYCAZ curtailed enrollment efforts and at the time of study termination on September 26th, 2021, only 4 patients had successfully completed the study. Of these, 1 subject each was enrolled in Cohorts 2 and 3; the remaining 2 subjects were in Cohort 4. PK samples from this study were analyzed using a validated bioanalytical method, and the data were used to update the existing population PK models for CAZ-AVI. Given the lack of sufficient PK data from this study, the Applicant relied primarily on the existing CAZ-AVI PK from the completed pediatric cUTI and cIAI studies to predict drug exposures in pediatric HABP/VABP patients.

Reviewer's Comment: *There is limited experience with PK extrapolation from pediatric patients with other infection types to those with nosocomial pneumonia. The most relevant example is provided by the FDA approval of Zosyn (piperacillin-tazobactam). Piperacillin-tazobactam was approved for the treatment of nosocomial pneumonia in adults in 2003, and at that time, the FDA was unable to enforce the Pediatric Rule (see PERC Meeting Minutes dated 05/05/2020). Consequently, there was no iPSP for the pediatric development program, and the planned pediatric studies did not include plans to specifically evaluate PK in pediatric patients with*

nosocomial pneumonia. Supported by single and multiple-dose PK studies in pediatric patients 2 months and older with complicated appendicitis and peritonitis, an intra-abdominal infection (IAI) indication was granted for pediatrics in 2005. Finally, in 2019, the nosocomial pneumonia indication was extended to pediatrics using PK data from the pediatric IAI program to inform dose selection, and a retrospective cohort analysis to support the safety of the recommended dosage regimen. Primary evidence of Zosyn's effectiveness for the treatment of nosocomial pneumonia in pediatric patients was based on extrapolation of efficacy from adult patients with nosocomial pneumonia to pediatric patients (which is consistent with the approach used in this current Avycaz® supplemental NDA). PK modeling-based analyses demonstrated similar drug exposures in adults and pediatric patients down to 2 months of age administered a dose of 80-100 mg/10-12.5 mg/kg every 6 h (for additional details, see the Clinical Pharmacology and Pharmacometrics Reviews from Dr. Tworzyanski, Dr. Jadhav and Dr. Nicasio).

15.5. Pharmacometrics Review

1. Population PK analysis

1.1 Review Summary

The Applicant's updated population pharmacokinetics (PopPK) analysis for ceftazidime (CAZ)-avibactam (AVI) in children with nosocomial pneumonia (NP) with an updated dataset, used to justify NP pediatric dosage for subgroups (3 months to less than 6 months, 6 months to less than 2 years, 2 years to less than 18 years), is acceptable for predicting exposures in the general pediatric population for Probability of Target Attainment (PTA) analyses and descriptive labeling. Two limitations have been identified: 1) There are only 4 NP pediatric subjects, so the pediatric PK is primarily informed by the cUTI/cIAI pediatric data and adult data. There appears to be no common departure from the population PK prediction for these individuals and the inclusion of these data did not impact the final parameter estimates. Therefore it appears reasonable to leverage on the cUTI /cIAI pediatric PK to inform the NP population. 2) The model assumes a common between-subject variability for pediatrics and adults to inform the moderate and severe renal impairment populations in pediatrics and there are data from only 2 pediatric patients with moderate and none with severe renal impairment. The reviewer applied model simulations and performed a sensitivity analysis to evaluate whether increased variability would have a negative impact on the PTA. Based on the results of this analysis and given that renal impairment leads to an increase in exposure, it appears that the inability to capture the between subject variability does not impact dose selection. Therefore, the reviewer's independent assessment of PK exposures and PTA in virtual pediatric patients with NP supports the proposed NP pediatric dosage shown in Table 2.

The model structure and covariates applied in this application were previously reviewed and found acceptable for the labeling of AVI and CAZ in adult patients with cUTI/cIAI. etails for that review are in the multi-disciplinary unireview in DARRTs dated 3/13/2019 for the pediatric cUTI and cIAI supplements. This submission updates that model by including the PK data from the 4 pediatric subjects in Study 1025. The comparison of the updated model and the previously

accepted model are shown in Table 15 and Table 16. The parameters are nearly identical. As such the PopPK model was not extensively reviewed again for structure and covariates.

Table 12: Specific Comments on Applicant's Final Population PK model

Utility of the final model		**Reviewer's Comments**
Intrinsic factor: **Body weight**	Body weight, renal maturation (in subjects ≤ 2 years of age only) and nCrCL[11] (in subjects > 2 years of age only) were the key covariates predicting the clearance (CL) of both CAZ and AVI.	The reviewer performed simulation to predict exposure and PTA based on PopPK model and virtual NP pediatric dataset. The proposed dosage, outlined in Table 2, for NP pediatrics is acceptable.
Renal Impairment	Body weight, renal maturation (in subjects ≤ 2 years of age only) and nCrCL (in subjects > 2 years of age only) were the key covariates predicting the clearance (CL) of both CAZ and AVI.	The proposed dose for renal impairment, also outlined in Table 2 is acceptable. Sensitivity analysis and PK exposures support a favorable PTA analysis.
Infection types, Race, Ventilator, APACHE	These intrinsic factors were included as covariates but dose adjustment was not proposed for differences in these factors.	• Infection types and race were covariates of CL and central volumes (Vc) in CAZ and AVI. • Ventilator-associated bacterial pneumonia (Y/N) is a covariate in CAZ and AVI on Vc. • APACHE score (Acute physiology and chronic health evaluation) is identified as a covariate on Vc in AVI. • While their relationships were significant on the CL and V parameters, the conclusion that no dose adjustment is warranted for them is acceptable.

1.2 Introduction

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

- Update the previously developed CAZ and AVI PopPK models with an updated dataset that includes additional individual CAZ and AVI PK plasma concentration data from the pediatric subjects from phase 1 study C3591025.

[11] nCrCL: creatinine clearance normalized to 1.73m^2 body surface area

- Evaluate pediatric dose recommendations for pediatric patients with NP through simulations with the updated CAZ-AVI PopPK model parameter estimates. For each age group and renal function category (normal, mild, moderate, severe I, severe II and end stage renal disease (ESRD)), the maximum concentration at steady state (Cmax;ss), area under the plasma concentration-time curve over 24 hours at steady state (AUCss;0-24) and joint PTA for a MIC of 8 mg/L (CAZ) and a threshold of 1 mg/L (AVI) were assessed.

1.3 PopPK Model

Data

PopPK analysis datasets (one for CAZ and the other for AVI analysis) were generated by combining the final datasets from the previous PopPK analysis for CAZ and AVI reported in CAZ-MS-PED-02 (link) and the PK data from study 1025 (C3591025).

Table 13: Demographic , Baseline Characteristics, and Dose Administered for Subjects in Study 1025

ID	COH	Age(y)	CAZ Dose (mg)	AVI Dose (mg)	WT	BSA	nCrCL	Sex	Race
(b) (6)	2	(b) (6)	1975.2	493.8	39.5	1.27	151.46		(b) (6)
	3		800	200	16	0.71	143.46		
	4A		532	133	10.63	0.52	143.75		
	4B		285	71.3	5.7	0.34	NA		
(b) (4)			Line 1 substituted.						

Abbreviations: COH = study cohort, CAZ = Ceftazidime, AVI = Avibactam, WT = body weight, BSA = body surface area, nCrCL = creatinine clearance normalized to 1.73m^2 body surface area, NA = not available

Source: Applicant's report, Page 16 (link).

Reviewer's Comment: The update to the PopPK model from study 1025 includes only four subjects, shown in Table 13.

1.4 Summary of simulated exposures and PTA

In the Applicant's simulation, a virtual NP pediatric dataset and Nonlinear mixed effect modeling (NONMEM) codes were used to predict exposures and PTA for pediatric patients with NP. The virtual NP pediatric dataset demographic information, such as weight, age, race, were obtained from the PopPK dataset, Centers for Disease Control and Prevention (CDC) and publications. The virtual patients that do not have nCrCL were randomly assigned various nCrCL values to generate NP pediatric data with different renal functions. The resulting pediatric post hoc inter-individual variances (IIV) in the final Pop PK model were assigned to virtual NP

patients that do not have IIV. Therefore, IIV of the virtual NP pediatric dataset are only from the pediatric post hoc IIV, which are smaller than those of the PopPK model that are based on both adults and pediatrics data. The generated virtual pediatric dataset was used to simulate exposures and PTA for pediatric patients with NP and varying renal function.

The summary of simulated PK exposures and PTA, for the T4 target, for pediatrics patients with NP and varying degrees of renal function are shown in Table 14. The T4 target is defined to be 50% fT > MIC (percent of time of a dosing interval with a free drug concentration above the minimum inhibitory concentration) of 8 mg/L for CAZ (free fraction: 0.85) and 50% fT > CT (percent of time of a dosing interval with a free drug concentration above a threshold concentration) of 1 mg/L for AVI (free fraction: 0.92). PTA (> 90%) was achieved in pediatric patients with NP with the doses currently approved for complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI) in pediatric patients with various degrees of renal function.

Table 14. Summary of Simulated (n = 1000) Cmax, ss, Cmin, ss, AUCss, 0-24 and PTA for the PKPD target T4[a] at CAZ-AVI MIC of 8 mg/L in Pediatric and Adult Subjects with NP

Age Group	nCrCL Category	Dose[b] (CAZ/AVI)	CAZ $C_{max,ss}$ [mg/L]	CAZ $C_{min,ss}$ [mg/L]	CAZ $AUC_{ss,0-24}$ [mg.h/L]	AVI $C_{max,ss}$ [mg/L]	AVI $C_{min,ss}$ [mg/L]	AVI $AUC_{ss,0-24}$ [mg.h/L]	Joint PTA [%]
3 to <6m	Normal	40/10	70.9 (18.9)	5.68 (99.6)	727 (27.8)	13.3 (46)	0.401 (138)	117 (40.3)	99.5
6 to <12m	Normal	50/12.5	80.1 (19)	4.1 (122)	755 (28)	15.4 (45.6)	0.316 (155)	129 (40.4)	98.1
1 to <2y	Normal	50/12.5	75.9 (18.9)	3.01 (132)	684 (27.7)	14.9 (45.3)	0.264 (160)	122 (40.3)	94.1
2 to <6y	Normal	50/12.5	77.2 (21.5)	3.02 (137)	690 (28.7)	14.5 (45.7)	0.235 (170)	116 (40.8)	91.5
6 to <12y	Normal	50/12.5	81.8 (20.6)	5.3 (124)	798 (29.8)	15.8 (40.3)	0.462 (133)	136 (36.8)	96.9
12 to <18y	Normal	50/12.5	70.7 (25.5)	6.9 (90.2)	740 (31.9)	13.1 (64.3)	0.587 (85.2)	118 (50.7)	99.7
Adults	Normal	2000/500	65.8 (29.7)	7.78 (93.7)	713 (39)	10.6 (72.4)	0.776 (95.9)	105 (66)	96.2
2 to <6y	Mild	50/12.5	98.6 (22.9)	10.6 (97.3)	1070 (31.6)	17.8 (48.4)	0.762 (135)	163 (43.6)	100
6 to <12y	Mild	50/12.5	105 (21.6)	16.1 (93.4)	1240 (32.9)	19.4 (41.2)	1.31 (110)	191 (38.6)	100
12 to <18y	Mild	50/12.5	89.3 (26.7)	17.6 (72.5)	1120 (34.5)	15.7 (65.9)	1.35 (80.5)	161 (53.5)	100
Adults	Mild	2000/500	84.2 (31.3)	19.3 (74.4)	1100 (40.6)	12.9 (75.3)	1.76 (83.9)	148 (68.3)	99
2 to <6y	Moderate	25/6.25	64.9 (23.3)	15.3 (67.9)	866 (32.2)	11.8 (49)	1.49 (86)	134 (43.8)	100

Age Group	nCrCL Category	Dose[b] (CAZ/AVI)	CAZ $C_{max,ss}$ [mg/L]	CAZ $C_{min,ss}$ [mg/L]	CAZ $AUC_{ss,0-24}$ [mg.h/L]	AVI $C_{max,ss}$ [mg/L]	AVI $C_{min,ss}$ [mg/L]	AVI $AUC_{ss,0-24}$ [mg.h/L]	Joint PTA [%]
6 to <12y	Moderate	25/6.25	69.6 (22.7)	20.7 (64.8)	999 (32.9)	12.8 (41)	2.18 (72)	155 (38.4)	100
12 to <18y	Moderate	25/6.25	60 (27.6)	21.1 (57.1)	908 (35.3)	10.5 (64.3)	2.06 (63.8)	132 (53.2)	99.8
Adults	Moderate	1000/250	56.7 (32.3)	21.9 (58.4)	884 (40)	8.63 (75.1)	2.33 (66.5)	120 (66.6)	99
2 to <6y	Severe I	19/4.75	58.1 (23.3)	14.8 (69)	776 (33.8)	10.9 (52.1)	1.5 (90.9)	121 (45.6)	99.8
6 to <12y	Severe I	19/4.75	62.1 (24)	19.8 (66.2)	899 (35.5)	11.8 (43.2)	2.2 (74.8)	142 (40.6)	100
12 to <18y	Severe I	19/4.75	52.6 (29.8)	19.6 (59.7)	803 (38.8)	9.5 (67)	2 (69.2)	118 (55.3)	99.6
Adults	Severe I	750/187.5	49.8 (33.7)	20.3 (62.7)	783 (43.2)	7.73 (79.7)	2.25 (72)	108 (70.2)	98.9
2 to <6y	Severe II	19/4.75	65.9 (25.8)	16.9 (75.7)	866 (38.4)	12.8 (54.3)	1.76 (109)	138 (48.8)	99.7
6 to <12y	Severe II	19/4.75	69.9 (25.2)	22.4 (71.6)	1000 (38.7)	13.7 (44.9)	2.56 (87.6)	160 (43.7)	99.9
12 to <18y	Severe II	19/4.75	59.1 (31.8)	22 (68.1)	891 (43.6)	11 (69.9)	2.3 (84.6)	133 (59.4)	99.6
Adults	Severe II	750/187.5	55.8 (36.2)	23 (68.2)	873 (47.4)	8.88 (84.2)	2.65 (79.9)	122 (73.5)	99
2 to <6y	ESRD	19/4.75	137 (109)	66.9 (204)	2340 (143)	13 (56)	1.49 (77)	129 (40.7)	100
6 to <12y	ESRD	19/4.75	144 (107)	79.5 (174)	2580 (133)	13.7 (45.1)	2.2 (63.1)	149 (35.1)	100
12 to <18y	ESRD	19/4.75	127 (109)	76.4 (165)	2360 (133)	11 (71.3)	2.02 (56.5)	124 (51.1)	100
Adults	ESRD	750/187.5	129 (118)	84 (171)	2490 (141)	8.77 (84.1)	2.38 (60.4)	115 (65.2)	99

(b) (4) Line 1 substituted.

nCrCL Category is based on nCrCL (mL/min/1.73m^2) values as follows: > 80 (normal), 51 - 80 (mild), 31 - 50 (moderate), 16 - 30 (severe I), 6 - 15 (severe II), <6 (ESRD).

Pharmacokinetic parameter values correspond to geometric mean (geometric CV%).

[a] Target T4 was defined to be 50 % fT > MIC of 8mg/L for CAZ and 50% $fT > C_T$ 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 the respective adult dose for each renal function category.

Abbreviations: $C_{max,ss}$ = maximum concentration at steady state, $C_{min,ss}$ = minimum concentration at steady state, $AUC_{ss,0-24}$ = area under the plasma concentration-time curve over 24 hours at steady state, PTA = probability of target attainment pharmacokinetic-pharmacodynamic (PKPD) = pharmacokinetic-pharmacodynamic, CAZ-AVI = Ceftazidime-Avibactam, MIC = minimum inhibitory concentration, NP = nosocomial pneumonia, nCrCL = creatinine clearance normalized to 1.73 m^2 body surface area, CAZ = Ceftazidime, AVI = Avibactam, ESRD = end stage renal disease.

Source: Applicant's report, Page 34-36 (link).

Reviewer comment:

The PopPK model estimated parameters of CAZ and AVI are almost exactly the same as those of the previous PopPK model in the CAZ-MS-PED-02 report shown in Table 15 and Table 16 because only four NP pediatric subjects were updated to the dataset. The previous PopPK model used for

dose selection for CAZ-AVI across pediatric age groups (birth to < 18 years) for patients with cIAI and cUTI caused by Gram-negative bacteria was found acceptable for PK analyses supporting PTA and descriptive labeling. Therefore, the PopPK model structure was not assessed in this review.

The majority of the PK predictions for NP pediatric subjects were also informed by PK data from the cUTI/cIAI population. First, the limited number of pediatric subjects with NP is generally insufficient to establish confidence around the mean exposure and also establish the PTA in pediatric patients with NP alone. The concern for sample size is in part based on the sample size requirement of FDA General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products Guidance for Industry[12]. This is further supported given lack of mechanism to suggest a difference in PK in different disease states and that the population prediction for the four pediatric subjects with NP appears to capture the central tendency of their data. As a result, population simulation and sensitivity analyses were performed by the reviewer, based on the PopPK model and virtual NP pediatric data, to assess exposure and PTA of NP pediatrics.

In the Applicant's simulation, the pediatric patients (age from 2 to less than 18) post hoc IIV (study 14 (Phase 1 single dose study in hospitalized pediatric patients with suspected or confirmed infection, 32 subjects), 15 (cIAI pediatric study, 61 subjects) , 16 (cUTI pediatric study, 67 subjects), 1025 (NP pediatric study, 4 subjects)) were assigned to virtual NP pediatric data with different renal functions that do not have IIV. Meanwhile, there are no pediatric patients (age from 2 to less than 18) with moderate renal impairment (only two subjects with moderate renal impairment; ID, (b) (6), age (b) (6) ID: (b) (6), ignored in NONMEM (no post hoc IIV)), no severe renal impairment and no end stage renal disease (ESRD) in the totality of pediatric post hoc IIV data shown in Table 19. Therefore, in the procedure to assign IIV to the virtual pediatric dataset with different renal functions without IIV, there is one assumption that virtual pediatric patients with different renal functions have similar IIV. However, in adult patients, the post hoc IIV of normal, mild, moderate, severe I, severe II renal impairment, and ESRD pediatrics are a little different, shown in Table 17 and Table 18. In addition, whether pediatric patients with NP have similar IIV among normal, mild, moderate, severe I, severe II renal impairment, and ESRD pediatric patients is unknown. Therefore, the justification for NP pediatric dosage with various renal impairment for descriptive labeling needs further investigation. Thus, the reviewer independently assessed the exposure and PTA based on simulation by PopPK model parameter estimates and virtual pediatric NP dataset, which was generated only from pediatric data in PopPK dataset by changing infection types to NP. Furthermore, the sensitivity assessment of virtual pediatric patients with NP (age from 2 to less than 18) with different renal functions showed that the dosage approved for pediatric patients with cIAI and cUTI (age from 2 to less than 18) and with different renal functions can achieve

[12] General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products 2022 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products

over 90% PTA, which showed that the dosage is acceptable for pediatric patients (age from 2 to less than 18) with NP.

Table 15. Final CAZ PopPK Model Parameter Estimates Comparison Between Dataset Without Study 1025 and Datasets With Study 1025

Parameter	Estimate with study 1025	Estimate without study 1025
nCrCL effect on CL		
Slope 1: nCrCL < 100 mL/min; Slope 1 x nCrCL	0.01030360 Fixed	0.01030360 Fixed
Slope 2: nCrCL >= 100 mL/min; Slope 1 x 100 + Slope 2 x (nCrCL-100)	0.00125182 Fixed	0.00125182 Fixed
ϑ_1: CL (L/h)	9.12	9.13
ϑ_2: Vc (L)	11.2	11.2
ϑ_3: Q (L/h)	5.31	5.33
ϑ_4: Vp (L)	6.52	6.53
ϑ_{13}: Maximum covariate effect for WT on CL as an E_{max} function	1.50	1.50
ϑ_{15}: WT at half-maximal effect of WT on CL as part of an E_{max} function	53.4	53.4
ϑ_{16}: Population effect on CL for patients with cIAI (CL x ϑ_{16})	1.33	1.33
ϑ_{17}: Population effect on CL for patients with NP (CL x ϑ_{17})	1.10	1.10
ϑ_{18}: Race effect on CL for ASN (CL x (1 + ϑ_{18}))	-0.137	-0.136
ϑ_{19}: Race effect on CL for CHN (CL x (1 + ϑ_{19}))	-0.0846	-0.0843
ϑ_{20}: Population effect on Vc for patients with cUTI (Vc x ϑ_{20})	1.50	1.50
ϑ_{21}: Population effect on Vc for patients with cIAI or NP (Vc x ϑ_{21})	1.83	1.84
ϑ_{22}: Population effect on Vc for presence of ventilator (Vc x (1 + ϑ_{22})	0.203	0.202
ϑ_{23}: Race effect on Vc for ASN CHN and JPN (Vc x (1 + ϑ_{23}))	-0.137	-0.135
ETA values		
η CL^2	0.153	0.154
η Vc^2	0.108	0.109
η Q^2	0.207	0.203
η Vp^2	0.0235	0.0236
Residual Error		
Proportional variability Phase 1	0.172	0.172
Additive variability Phase 1 (ng/mL)	125	125
Proportional variability Phase 2 or 3	0.374	0.374
Additive variability Phase 2 or 3 (ng/mL)	2560	2560

Abbreviations: IIV = inter-individual variance, nCrCL = creatinine clearance normalized to 1.73 m^2 body surface area, ϑ =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.
Source: caz-ms-ped-02 report page 85 (link) and Applicant's report, Page 19 (link).

Table 16. Final AVI PopPK Model Parameter Estimates Comparison Between Dataset Without Study 1025 and Datasets With Study 1025

Parameter	Estimate with study 1025	Estimate without study 1025
ϑ_1: CL (L/h)	11.8	11.7
ϑ_2: Vc (L)	13.8	13.6
ϑ_4: Q (L/h)	7.71	7.74
ϑ_3: Vp (L)	8.18	8.18
ϑ_5: Relative CL estimate for patients with ESRD; CL x ϑ_5	0.0651	0.0651
ϑ_6: CL estimate for dialysis patients (L/h)	23.3	23.3
ϑ_7: Power nCrCL on CL	1.02	1.02
ϑ_8: Linear nCrCL on CL	0.0033	0.00332
ϑ_9: Population effect on Vc (cIAI) Phase 2 (Vc x (1 + ϑ_9))	1.92	1.96
ϑ_{10}: Population effect on CL (cIAI) adult Phase 2 (CL x (1 + ϑ_{10}))	0.418	0.422
ϑ_{11}: Population effect on Vc (cUTI) (Vc x (1 + ϑ_{11}))	0.512	0.521
ϑ_{12}: Population effect on Vc for patients with cIAI or NP (Vc x ϑ_{12})	0.323	0.331
ϑ_{15}: APACHE on Vc	-0.181	-0.181
ϑ_{28}: Ventilator on Vc	0.238	0.238
ETA values		
η CL^2	0.336	0.336
η Vc-η CL	0.156	0.155
η Vc^2	0.689	0.689
η Vp-η CL	0.584	0.583
η Vp-η Vc	-0.0649	-0.0698
η Vp^2	1.25	1.24
η Q-η CL	1.05	1.06
η Q-η Vc	-0.212	-0.215
η Q-η Vp	2.28	2.29
η Q^2	4.24	4.28
Residual Error		
ϑ_{17} Proportional variability Phase 1	0.176	0.176
ϑ_{18} Additive variability Phase 1 (ng/mL)	44.6	44.5
ϑ_{19} Proportional variability Phase 2	0.519	0.518
ϑ_{20} Proportional variability Phase 3	0.387	0.387

Abbreviations: AVI = Avibactam, 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 m^2 body surface area, ϑ = typical value of PK parameter, cIAI = complicated intra-abdominal infection , cUTI = tract infection, NP = nosocomial pneumonia.
Source: Applicant's report, Page 26 & 28 (link).

Table 17. Adult Post-Hoc AVI Different Inter-Individual Variance With Various Renal Functions

Renal function	Subject	Ω_{ETA1}	Ω_{ETA2}	Ω_{ETA3}	Ω_{ETA4}	SD_{ETA1}	SD_{ETA2}	SD_{ETA3}	SD_{ETA4}
Normal >80	1374	0.274	0.355	0.939	3.16	0.523	0.596	0.969	1.778
Mild 51-80	657	0.398	0.423	1.24	4.08	0.631	0.65	1.11	2.02
Moderate 31-50	180	0.329	0.245	1.04	3.44	0.57	0.494	1.02	1.85
Severe I 16-30	33	0.285	0.31	0.876	2.95	0.533	0.555	0.936	1.72
Severe II 6-15	4	0.222	0.031	0.828	2.74	0.471	0.177	0.91	1.655
ESRD <6	2	0.321	0.031	1.11	3.638	0.566	0.175	1.06	1.91

Note: subject: subject number; Ω: variance ; SD standard deviation; ETA1: inter-individual variability on CL; ETA2: inter-individual variability on Vc; ETA3: inter-individual variability on Vp; ETA4: inter-individual variability on Q; The mean ETAs are assumed to be 0. All the numbers are rounded to 3 decimal places.
Source: reviewer independent assessment.

Table 18. Adult Post-Hoc CAZ Different Inter-Individual Variance With Various Renal Functions

Renal function	Subject	Ω_{ETA1}	Ω_{ETA2}	Ω_{ETA3}	Ω_{ETA4}	SD_{ETA1}	SD_{ETA2}	SD_{ETA3}	SD_{ETA4}
Normal >80	1150	0.119	0.033	0.001	0.013	0.346	0.182	0.033	0.114
Mild 51-80	633	0.122	0.02	0	0.003	0.35	0.144	0.009	0.053
Moderate 31-50	170	0.197	0.014	0	0.002	0.444	0.12	0.006	0.042
Severe I 16-30	18	0.091	0.009	0	0.001	0.302	0.095	0.003	0.023
Severe II 6-15	3	0.317	0.024	0	0.001	0.563	0.154	0.006	0.034
ESRD <6	2	0.152	0.011	0	0.0012	0.39	0.105	0.002	0.04

Note: subject: subject number; Ω: variance ; SD standard deviation; ETA1: inter-individual variability on CL; ETA2: inter-individual variability on Vc; ETA3: inter-individual variability on Vp; ETA4: inter-individual variability on Q; The mean ETAs are assumed to be 0. All the numbers are rounded to 3 decimal places.
Source: reviewer independent assessment.

Data

In the 164 pediatric patients, 2 subjects (ID: (b) (6)) whose nCrCL values are not available were excluded from assessment. The renal functions of pediatric patients listed in Table 19 showed that there are 32 subjects with normal renal function in study 14, 9 subjects with mild renal impairment and 51 subjects with normal renal function in study 15, 22 subjects with mild renal impairment, 43 subjects with normal renal function and 2 subjects with moderate renal impairment in study 16, and 3 subjects with normal renal function in study 1025. In age from 2 to 17 years and from 6 months to 2 years, there is only one subject with

moderate renal impairment, shown in Table 20. Therefore, moderate renal impairment is NOT included in the assessment. The demographic characteristics for the 162 pediatric subjects are shown in Table 21.

Table 19. Renal Function Characteristics For Pediatric Subjects

STDY	Renal Function	Subject
14	Normal nCrCL >80	32
15	nCrCL (not available)	1
15	Mild nCrCL 51-80	9
15	Normal nCrCL >80	51
16	Mild nCrCL 51-80	22
16	Moderate nCrCL 31-50	2
16	Normal nCrCL >80	43
1025	nCrCL (not available)	1
1025	Normal nCrCL >80	3
Total		164

Note: Study 14 (D4280C00014): a Phase 1, open-label, single-dose study in hospitalized pediatric patients from 3 months to < 18 years of age who received systemic antibiotic therapy for suspected or confirmed infection.
Study 15 (D4280C00015/C3591004): a Phase 2, single-blind, randomized, multicenter, active-controlled, multiple-dose study conducted to evaluate the safety, tolerability, PK, and efficacy of CAZ-AVI when given in combination with metronidazole, and when compared with meropenem, in children with cIAIs from 3 months to < 18 years of age.
Study 16 (D4280C00016/C3591005): a Phase 2, single-blind, randomized, multicenter, active-controlled multiple-dose study conducted to evaluate the safety, tolerability, PK, and efficacy of CAZ-AVI compared with cefepime in children with cUTIs from 3 months to < 18 years of age.
Abbreviations: nCrCL = creatinine clearance normalized to 1.73m^2 body surface area;
Source: reviewer independent assessment and study description from CAZ-MS-PED-02 report page 5 (link).

Table 20. Summary of Renal Function Per Age Group

Age	nCrCL	Subject
2 to 17 years	Mild 51-80	19
2 to 17 years	Moderate 31-50	1
2 to 17 years	Normal >80	107
3 to 6 months	Mild 51-80	1
3 to 6 months	Normal >80	6
6 month to 2 years	Mild 51-80	11
6 month to 2 years	Moderate 31-50	1
6 month to 2 years	Normal >80	16

Abbreviations: nCrCL = creatinine clearance normalized to 1.73m^2 body surface area;
Source: reviewer independent assessment.

Table 21. Demographic and Baseline Characteristics For Pediatric Subjects (mean (min~max))

STDY	TYPE	Subject	Age (year)	WT	BSA	nCrCL
16	cUTI	67	6 (0.2~ 17.7)	24.5 (4.1~ 86.6)	0.9 (0.3~ 2)	95.2 (43~ 176)
15	cIAI	60	10.3 (3~ 17)	40.3 (15.4~ 80)	1.3 (0.7~ 2)	117.6 (59~ 279)
1025	NP	3	5.4 (1.8~ 9.4)	22 (10.6~ 39.5)	0.8 (0.5~ 1.3)	146.2 (143.5~ 151.5)
14	infection	32	6.9 (0.3~ 17.3)	25.4 (5.4~ 60.5)	0.9 (0.3~ 1.7)	149.9 (85.5~ 489.4)
total		162	7.8 (0.2~ 17.7)	30.5 (4.1~ 86.6)	1 (0.3~ 2)	115.3 (43~ 489.4)

Abbreviations: WT = body weight (kg); BSA = body surface area (m^2); nCrCL = creatinine clearance normalized to 1.73m^2 body surface area;
Source: reviewer independent assessment.

Model codes required by mrgsolve R package were based on PopPK models. Meanwhile, all the pediatric subjects were set to be NP patients and the individual prediction (IPRED) was calculated based on the population predictions (PRED) and pediatric post hoc inter-individual variabilities, which are smaller than those in PopPK inter-individual variability due to inclusion of adult patients. There are 157 subjects for CAZ and 156 subjects for AVI with post hoc inter-individual variabilities, which is different from the total pediatric subject numbers due to subject exclusion in NONMEM. The PTA was calculated based on 50% fT > MIC of 8mg/L for CAZ (free fraction: 0.92) and 50% fT > CT of 1 mg/L for AVI (free fraction: 0.85).

The dosage is AVYCAZ 62.5 mg/kg (Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg) for 6 months to less than 2 years, AVYCAZ 62.5 mg/kg (Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg to a maximum dose of ceftazidime 2 grams and avibactam 0.5 grams) for 2 years to less than 18 years with eGFR greater than 50 mL/min/1.73 m^2 and AVYCAZ 50 mg/kg (Ceftazidime 40 mg/kg and avibactam 10 mg/kg) for 3 months to less than 6 months with eGFR greater than 50 mL/min/1.73 m^2.

The simulated NP pediatric exposure and PTA values are shown in Table 22, in which the total daily area under the plasma concentration-time curve at steady state (AUCss, 0-24) and Cmax under steady state (Cmax,ss) for CAZ and AVI are lower than those in adult NP patients in Table 23. Meanwhile, PTA values for different age groups are greater than 90%. Therefore, the pediatric (eGFR greater than 50 mL/min/1.73 m^2) dosage of AVYCAZ 62.5 mg/kg (Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg) for 6 months to less than 2 years, AVYCAZ 62.5 mg/kg (Ceftazidime 50 mg/kg and avibactam 12.5 mg/kg to a maximum dose of ceftazidime 2 grams and avibactam 0.5 grams) for 2 years to less than 18 years and AVYCAZ 50 mg/kg (Ceftazidime 40 mg/kg and avibactam 10 mg/kg) for 3 months to less than 6 months is acceptable.

Table 22. Summary of Simulated AUCss,0-24, Cmax,ss for AVI and CAZ in NP Pediatrics

Age	2 to 17 years	6 month to 2 years	3 to 6 months
AVI $AUC_{ss,0\text{-}24}$ (ug/mL*hr)	129 (40)	125.9 (41.8)	135.7 (27.3)
AVI $C_{max,ss}$ (ug/mL)	14.8 (42.3)	14.2 (36.1)	14.8 (29.6)

CAZ AUCss,0-24 (ug/mL*hr)	788 (27.3)	796.4 (24.2)	679.8 (21.8)
CAZ Cmax,ss (ug/mL)	82.2 (18.7)	82.3 (11.6)	70.2 (14.6)
Joint PTA (%)	99.2	96.2	100

Abbreviations: $AUC_{ss,0-24}$ = total daily area under the plasma concentration-time curve at steady state; AVI = avibactam; CAZ = ceftazidime; $C_{max,ss}$ = maximum plasma concentration at steady state; PTA = probability of target attainment. Note: Values are the geometric mean (%CV).
Source: reviewer independent assessment.

Table 23. Summary of Model Predicted AUCss,0-24, Cmax,ss, and Cmin,ss for AVI and CAZ in Adult cUTI, cIAI, and NP Patients in the Analysis Dataset

Parameter	cUTI	cIAI	NP
Number of subjects (AVI/CAZ)	647/638	703/697	413/413
AVI $AUC_{ss,0-24}$ (ug/mL*hr)	139 (72.9)	133 (67.4)	174 (81)
AVI $C_{min,ss}$ (ug/mL)	1.53 (147)	1.12 (134)	2.27 (134)
AVI $C_{max,ss}$ (ug/mL)	12.3 (70.2)	12.9 (67.6)	14.7 (77)
CAZ $AUC_{ss,0-24}$ (ug/mL*hr)	973 (44.7)	722 (44.2)	936 (50.4)
CAZ $C_{min,ss}$ (ug/mL)	14.4 (108)	8.2 (106)	14.7 (108)
CAZ $C_{max,ss}$ (ug/mL)	80.7 (30.9)	66.2 (31.1)	74.8 (37.9)
Joint PTA (%)	98.7	98.4	99

Abbreviations: $AUC_{ss,0-24}$ = total daily area under the plasma concentration-time curve at steady state; AVI = avibactam; CAZ = ceftazidime; $C_{max,ss}$ = maximum plasma concentration at steady state; $C_{min,ss}$ = minimum plasma concentration at steady state; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; NP = nosocomial pneumonia; PTA = probability of target attainment.
Note: Values are the geometric mean (%CV). $AUC_{ss,0-24}$ is obtained by multiplying $AUC_{ss,0-8}$ from a single end of infusion. $C_{min,ss}$ is obtained 8 hours after the start of infusion.
Source population-modeling-analysis-report-caz-ms-ped-02 report page 117 (link)

Sensitivity assessment on NP pediatric patients with renal impairment (age from 2 to less than 18).

There are no data available from pediatric patients with varying degrees of renal function in the PopPK dataset and whether pediatric patients with NP and different renal functions have similar IIV is unknown. Therefore, the reviewer performed a sensitivity analysis to explore this further. The IIV of adults with varying degrees of renal functions were used to predict IIV of NP pediatrics with varying degrees of renal functions. In adult patients, the post hoc IIV of normal, mild, moderate, severe I, severe II renal impairment, and ESRD pediatrics are a little different, shown in Table 17 and Table 18. The approved dosage for cIAI and cUTI pediatrics with renal impairment 2 years and older shown in Table 24. Additionally, given there are limited data in pediatric patients with renal impairment to justify dosing in this population, a sensitivity assessment for virtual NP pediatrics with renal impairment may provide some confidence in the PTA assessment.

Table 24. Dosage for NP in Pediatric Patients 2 years and Older with Renal Impairment

Estimated eGFR (mL/min/1.73m^2)	Dose for AVYCAZ (ceftazidime and avibactam)	Frequency
31 to 50	AVYCAZ 31.25 mg/kg to a maximum of 1.25 grams (Ceftazidime 25 mg/kg and avibactam 6.25 mg/kg to a maximum dose of ceftazidime 1 gram and avibactam 0.25 grams)	Every 8 hours
16 to 30	AVYCAZ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 12 hours
6 to 15	AVYCAZ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 24 hours
Less than or equal to 5	AVYCAZ 23.75 mg/kg to a maximum of 0.94 grams (Ceftazidime 19 mg/kg and avibactam 4.75 mg/kg to a maximum dose of ceftazidime 0.75 grams and avibactam 0.19 grams)	Every 48 hours

Source labeling (link)

The rationale for the sensitivity assessment is that if the omegas of post hoc IIV of adults with normal renal function are higher than those of adults with renal impairment, the post hoc IIV of pediatric patients with normal renal function will be allowed to be assigned to virtual pediatric patients with renal impairment without IIV. Otherwise, the leveraged post hoc IIV of pediatric patients with normal renal functions can be assigned to virtual pediatric patients with renal impairment without IIV. The current approach leverages the root of omega ratios of adults with renal impairment to adults with normal renal function. In the similar way, the post hoc IIV of pediatric patients with mild renal function is assigned to virtual pediatric patients with moderate, severe I, severe II renal impairment and ESRD without IIV by utilizing the ratios of adults with renal impairment (moderate, severe I, server II renal impairment and ESRD) to adults with mild renal impairment, if the omegas of post hoc IIV of adults with moderate, severe I, server II renal impairment and ESRD are higher than those of adults with mild renal function. The results are shown in Table 25, which showed that AUCss,0-24 and Cmax,ss in pediatric patients with NP and moderate, severe I and severe II renal impairments are smaller than those in adult patients with NP respectively shown in Table 23 (AUCss,0-24 and Cmax,ss of AVI and CAZ of NP adults respectively: 174, 14.7, 936 and 74.8). The AUCss,0-24 (134.9) and Cmax,ss (12.1) in ESRD of NP pediatric patients of AVI is smaller than those in NP adults (AUCss,0-24 (174), Cmax,ss (14.7)) with approved dosage for NP adults, and the AUCss,0-24 (1778) and Cmax,ss (106.7) in ESRD of NP pediatric patients of CAZ is smaller than those (AUCss, 0-24 (2490), Cmax,ss (115)) of adults in ESRD shown in Table 14 with approved dosage for adult with ESRD. Additionally, PTAs of NP pediatric patients with moderate, severe I, severe II renal impairment and ESRD are over 90%. Therefore, dosage shown in Table 24 is acceptable for virtual NP pediatric patients with moderate, severe I, severe II renal impairment and ESRD with age from 2 to less than 18.

Table 25. Summary of Simulated AUCss,0-24, Cmax,ss for AVI and CAZ in Virtual NP Pediatric Patients With Moderate, Severe I, Severe II Renal Impairment And ESRD (Age From 2 to Less Than 18)

	Moderate	Severe I	Severe II	ESRD
AVI $AUC_{ss,0-24}$ (ug/mL*hr)	140.7 (45.4)	129.1 (43.9)	146.8 (47.7)	134.9 (42.4)
AVI $C_{max,ss}$ (ug/mL)	11.4 (44.9)	10.5 (43.4)	12.2 (44.4)	12.1 (46.1)
CAZ AUCss,0-24 (ug/mL*hr)	912.4 (38.6)	821.9 (33.8)	888.8 (52.8)	1778 (79.6)
CAZ Cmax,ss (ug/mL)	66 (25.7)	59 (22.6)	66.6 (31.1)	106.7 (54.4)
Joint PTA (%)	100	99.2	97.5	100

PTA = probability of target attainment.; Values are the geometric mean (%CV).
Source: reviewer independent assessment.

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/s/

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