NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number	NDA 206829/S-023
Priority or Standard	Priority
Submit Date	11/11/2025
Received Date	11/12/2025
PDUFA Goal Date	5/12/2026
Division/Office	Division of Anti-Infectives (DAI)/Office of Infectious Diseases (OID)
Review Completion Date	5/11/2026
Established/Proper Name	ceftolozane and tazobactam
Trade Name	ZERBAXA
Pharmacologic Class	A combination of a cephalosporin and a β-lactamase inhibitor
Code name	MK-7625A
Applicant	Cubist Pharmaceuticals, LLC, a subsidiary of Merck & Co., Inc.
Dosage form	Powder for injection, for intravenous use
Applicant proposed Dosing Regimen	Intravenous infusion 60 mg/kg (40 mg/kg ceftolozane and 20 mg/kg tazobactam) up to a maximum dose of 3 g (2000 mg ceftolozane and 1000 mg tazobactam) every 8 hours by intravenous infusion over 1 hour for 8 to 14 days
Applicant Proposed Indication(s)/Population(s)	Treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in pediatric patients from birth up to 18 years of age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Nosocomial pneumonia (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in pediatric patients (at least 32 weeks gestational age)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	425464007 | Nosocomial pneumonia (disorder)
Recommended Dosing Regimen	Intravenous infusion 60 mg/kg (40 mg/kg ceftolozane and 20 mg/kg tazobactam) for pediatric patients from at least 32 weeks gestational age to less than 2 years and 75 mg/kg (50 mg/kg ceftolozane and 25 mg/kg tazobactam) for pediatric patients from 2 years and older up to a maximum dose of 3 g

	(2 g ceftolozane and 1 g tazobactam) every 8 hours by intravenous infusion over 2 hours for 8 to 14 days

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OCP=Office of Clinical Pharmacology
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DIDP= Division of Infectious Disease Pharmacology
DMEPA=Division of Medication Error Prevention and Analysis
DPM= Division of Pharmacometrics
DRISK=Division of Risk Management
DPMH=Division of Pediatrics and Maternal Health

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BLA	biologics license application
CDAD	*Clostridioides difficile*-associated diarrhea
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
cIAI	complicated intra-abdominal infections
CMC	chemistry, manufacturing, and controls
CRE	carbapenem-resistant Enterobacterales
CRF	case report form
CSR	clinical study report
CSS	Controlled Substance Staff
cUTI	complicated urinary tract infections
C/T	ceftolozane/tazobactam
DAI	Division of Anti-Infectives
DIDP	Division of Infectious Disease Pharmacology
DILI	drug-induced liver toxicity
DPM	Division of Pharmacometrics
DPMH	Division of Pediatric and Maternal Health
EA	environmental assessment
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ELF	epithelial lining fluid
EOT	end of treatment visit
ESBL	extended-spectrum β-lactamases
FDA	Food and Drug Administration
FT	Fast Track
GA	gestational age
GCP	good clinical practice
HABP	hospital-acquired bacterial pneumonia
HD	hemodialysis
ICH	International Conference on Harmonisation
IHD	intermittent hemodialysis
IND	Investigational New Drug

IPSP	initial pediatric study plan
ITT	intent to treat
MDR	multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MERO	meropenem
mITT	modified intent to treat
MODS	multiple organ dysfunction syndrome
MTZ	metronidazole
NDA	new drug application
NP	nosocomial pneumonia
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OID	Office of Infectious Diseases
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PBP	penicillin binding protein
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PWR	pediatric written request
QIDP	Qualified Infectious Disease Product designation
REMS	risk evaluation and mitigation strategy
RTI	respiratory tract infection
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TAZ	tazobactam
TEAE	treatment emergent adverse event
TOL	ceftolozane
ULN	upper limit of normal
UTI	urinary tract infection
VABP	ventilator-associated bacterial pneumonia
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

ZERBAXA (ceftolozane/tazobactam; C/T) combines ceftolozane (TOL), a cephalosporin with a 3'-aminopyrazolium structure, and tazobactam, which inhibits β-lactamase enzymes. This combination therapy targets gram-negative bacterial infections, particularly those involving multidrug-resistant *Pseudomonas aeruginosa* and Enterobacterales resistant to β-lactam antibacterials. The mechanism of action for TOL involves targeting critical penicillin-binding proteins (PBPs) which disrupt bacterial cell wall formation and lead to bacterial cell death. In *P. aeruginosa*, TOL demonstrates binding capacity to multiple essential PBPs, including 1b, 1c, and 3. Tazobactam (TAZ) functions as an irreversible β-lactamase inhibitor through covalent binding to both chromosomal and plasmid-mediated bacterial β-lactamases, preventing them from hydrolyzing and destroying TOL before it can reach PBP targets. It is effective against many class A β-lactamases, including ESBL (e.g., TEM, SHV, and CTX-M types) and some class C enzymes, which would otherwise compromise ceftolozane's antibacterial activity.

The Agency first approved ZERBAXA on December 19, 2014, for treatment of adult patients with complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI). The standard dosage for these indications is 1.5 g (1 g TOL and 0.5 g TAZ) administered intravenously over one hour, every eight hours. On June 3, 2019, the Agency approved a subsequent efficacy supplement (S-008) to expand the indicated use of ZERBAXA to include the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adult patients. This approval authorized an increased dosage regimen of 3 g (2 g TOL and 1 g TAZ) to support the therapeutic requirements of this expanded indication. Dosage adjustments are required for all adult indications in patients with renal impairment.

The Agency subsequently approved efficacy supplements (S-011 and S-012) on April 21, 2022, extending the approved indication of ZERBAXA to pediatric patients from birth to less than 18 years of age for the treatment of cIAI and cUTI. The approved pediatric dosage is 30 mg/kg (up to a maximum of 1.5 g) administered intravenously over one hour, every eight hours. However, prior to the current supplement, ZERBAXA was not indicated for use in pediatric patients with renal impairment, who have an eGFR 50 mL/min/1.73m^2 or less.

The present efficacy supplement is seeking an indication for the treatment of HABP and VABP in pediatric patients from birth up to 18 years of age. The Division's recommended indication is for treatment of HABP and VABP in pediatric patients (at least 32 weeks gestational age). This submission fulfills the Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) 3637-1: Conduct a safety and pharmacokinetic study in

HABP/VABP in children from birth to less than 18 years of age. In addition, the present submission seeks to propose dosage adjustments for pediatric patients (two years of age and older) with renal impairment across all indications including treatment of cIAI, cUTI, and HABP/VABP. This review will analyze the data submitted to support these proposed changes to the pediatric labeling.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence supporting ZERBAXA's approval for treating HABP/VABP caused by susceptible gram-negative organisms in pediatric patients (at least 32 weeks gestational age to <18 years) was derived from adult HABP/VABP study PN008 (CXA-NP-11-04), "A Prospective, Randomized, Double-blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/tazobactam Compared with Meropenem in Adult Patients with Ventilated Nosocomial Pneumonia," given that the disease mechanisms and causative pathogens are comparable between adult and pediatric populations. The proposed pediatric dosing regimen for HABP/VABP treatment, as well as the dosing modifications for renal impairment in pediatric patients over the age of 2 years, are further supported by population pharmacokinetic modeling, simulation studies, and probability of target attainment analyses (refer to Section 6.2 for further information).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

ZERBAXA (ceftolozane/tazobactam; C/T) is a combination of TOL, a cephalosporin with a 3'-aminopyrazolium structure that targets penicillin-binding proteins, specifically 1b, 1c and 3, and tazobactam, a β-lactamase inhibitor, which binds to both chromosomal and plasmid-mediated bacterial β-lactamases. ZERBAXA is approved for the treatment of cIAI and cUTI in adult and pediatric patients and for HABP/VABP in adult patients. In this supplemental NDA submission, the Applicant is seeking to expand the HABP/VABP indication to include pediatric patients (at least 32 weeks gestational age [GA] to less than 18 years of age) and expand dosing recommendations to pediatric patients 2 years and older with renal impairment across all indications, including cIAI, cUTI, and HABP/VABP.

Data from one phase 1, open-label, non-comparative study of pediatric patients from birth (>32 weeks gestational age and ≥7 days postnatal) to less than 18 years of age with HABP/VABP (Study P036: A Phase 1, open-label, non-comparative, multicenter clinical study to evaluate the safety, tolerability, and pharmacokinetics of C/T (MK-7625A) in pediatric participants with nosocomial pneumonia) was submitted to support the use of ZERBAXA in the proposed pediatric population. The open-label study enrolled 40 pediatric patients with the primary objective to evaluate the safety, tolerability and pharmacokinetic (PK) data of ZERBAXA in pediatric participants. The efficacy of ZERBAXA was extrapolated from the approval in adult patients with HABP/VABP. The dosing regimen studied was age and weight based with ZERBAXA 60 mg/kg (TOL 40 mg/kg and TAZ 20 mg/kg) for pediatric patients under the age of 12 years and ZERBAXA 3 g (TOL 2 g and TAZ 1 g) for pediatric patients 12 years and older. ZERBAXA was administered every 8 hours for 8 days to 14 days by IV infusion over 1 hour.

The safety profile of ZERBAXA observed in the pediatric study for HABP/VABP was consistent with the safety findings previously established in pediatric patients treated for cIAI and cUTI, as well as in adult patients with HABP/VABP. There were three deaths that occurred in this study, but these deaths were determined not to be attributable to C/T. Serious adverse events (SAE) were infrequent and there were no discontinuations due to adverse events. There were no concerning trends in laboratory values. There was one potential Hy's Law case reported, however this finding was attributed to the participant's underlying medical condition. The major risks identified with the use of ZERBAXA include anaphylaxis and *Clostridioides difficile*-associated diarrhea, however these adverse reactions were not identified in this study.

The efficacy of ZERBAXA for the proposed pediatric indication was extrapolated from the adult population, an approach justified by the sufficiently similar course of the disease and drug effects in both groups. The ZERBAXA dose of 60 mg/kg (40 mg/kg TOL and 20 mg/kg TAZ) given every 8 hours over a 1 hour infusion for pediatric patients 32 weeks gestational age to less than 2 years of age matched drug exposures

observed in adult patients with HABP/VABP. However, the clinical PK data revealed that drug exposures were lower in pediatric patients 2 years of age and older—specifically, 1.6-fold lower for TOL and 1.8-fold lower for TAZ median exposures (measured as AUC_{0-8}) compared to respective adult exposures. To address this discrepancy, additional PK modeling and simulations were performed. The modeling and simulation findings supported an adjustment of a 25% dose increase to ZERBAXA 75 mg/kg (50 mg/kg of TOL and 25 mg/kg of TAZ) given every 8 hours, combined with an extended infusion time of two hours in pediatric HABP/VABP patients aged 2 years and older. In this age group, the adjusted regimen is projected to increase exposures to achieve AUC_{0-8} and Cmax values for both drugs comparable to those in adult HABP/VABP patients. Importantly, simulation analyses suggest that the adjusted regimen for pediatrics 2 years and older does not increase the risk of exceeding the 95th percentile of adult Cmax and AUC_{0-8} values for either drug, thereby maintaining exposures within the established safety profile of both drugs. In pediatric patients less than 2 years of age, the originally proposed ZERBAXA dose of 60 mg/kg (40 mg/kg TOL and 20 mg/kg TAZ) given every 8 hours is recommended; however, an extended infusion time of two hours is recommended to mitigate medication errors. This extended infusion duration in pediatric patients at least 32 weeks gestational age to less than 2 years of age results in a reduction in Cmax but maintains AUC.

Overall, ZERBAXA has a favorable safety and efficacy profile for the treatment of HABP/VABP in pediatric patients from birth (at least 32 weeks GA) to less than 18 years of age. The risks associated with ZERBAXA 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	• Pediatric patients who develop bacterial pneumonia in hospital settings or associated with ventilator use (HABP/VABP) experience prolonged hospitalizations and elevated rates of illness and death, particularly among those receiving intensive care. The most frequently identified causative organisms are *Staphylococcus aureus*, gram-negative organisms like *Pseudomonas aeruginosa*, and members of the Enterobacterales family. • Drug-resistant gram-negative bacteria, especially carbapenem-resistant Enterobacterales (CRE) and difficult-to-treat *Pseudomonas aeruginosa*, represent a growing challenge given the limited availability of effective antimicrobial therapies for	• Infections due to HABP/VABP represent severe, potentially fatal conditions that contribute to morbidity and mortality in the pediatric population. • The rising prevalence of antimicrobial resistance, especially among gram-negative bacteria, poses a significant public health challenge due to the scarcity of effective therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	managing these infections.	
Current Treatment Options	• Antimicrobial agents authorized for pediatric HABP/VABP treatment encompass extended-spectrum penicillins, cephalosporins, beta-lactam/beta-lactamase inhibitor combinations, fluoroquinolones, carbapenems, monobactams, aminoglycosides, tetracyclines, and sulfonamides. • Novel antibacterial therapies recently authorized for pediatric use that may offer treatment alternatives for HABP/VABP infections caused by drug-resistant gram-negative organisms include ceftazidime-avibactam (approved in 2022) and imipenem/cilastatin/relebactam (approved in 2025). Of note, currently, meropenem/vaborbactam is not approved for treatment of HABP/VABP and cefiderocol is not approved for treatment of HABP/VABP in pediatric patients. • Despite these advances, additional therapeutic options are still needed for managing infections, including HABP/VABP caused by difficult-to-treat *Pseudomonas aeruginosa* and CRE.	• Multiple antimicrobial drug classes have received approval for managing severe infections in pediatric patients. Certain newly authorized antibacterial agents may offer therapeutic alternatives for infections caused by drug-resistant gram-negative organisms. Nevertheless, additional treatment options are still needed for multidrug-resistant (MDR) infections, particularly HABP/VABP cases caused by *Pseudomonas aeruginosa* and Enterobacterales.
Benefit	• The effectiveness and safety of ZERBAXA for pediatric patients ranging from newborns (at least 32 weeks GA) to those under 18 years of age with suspected or confirmed HABP/VABP is extrapolated from adult clinical data with ZERBAXA in HABP/VABP treatment, using pharmacokinetic bridging (matching AUC and Cmax values) to established adult exposure parameters. • Due to low drug exposures in pediatric patients 2 years of age and older with HABP/VABP, the recommended dose of C/T was	• The effectiveness of ZERBAXA for treating HABP/VABP in pediatric patients is substantiated by the Agency's previous determinations of ZERBAXA efficacy in adult patients with these infections, combined with pharmacokinetic and clinical evidence from pediatric trials. • The wide therapeutic index of β-lactams

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	increased by 25% combined with a longer infusion time (i.e., 2 hours) to match drug exposures in adult patients with HABP/VABP. For pediatric patients at least 32 weeks gestational age to less than 2 years of age, the original ZERBAXA dose is recommended with a longer infusion time (i.e., 2 hours) to mitigate medication errors.	and β-lactamase inhibitors allows for dosing adjustments to be made with a low risk of toxicity. • This class of antibacterials has a well-established safety profile.
Risk and Risk Management	• ZERBAXA did not demonstrate any novel safety issues in the pediatric population. No significant ZERBAXA-related risks in children requiring dedicated risk mitigation approaches have been identified.	• At present, product labeling and standard pharmacovigilance activities will sufficiently address communication and surveillance of safety issues associated with ZERBAXA use in pediatric patients.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	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):		
☒	**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 healthcare associated infections associated with significant morbidity and mortality worldwide. HABP is characterized as a bacterial lung infection developing more than 48 hours following hospital admission or occurring within 7 days post-discharge. VABP refers to bacterial pulmonary infections that develop in patients who have undergone intubation for longer than 48 hours. HABP/VABP infections are frequently encountered in United States healthcare settings and have been linked to prolonged hospitalizations, substantial economic costs, and mortality rates spanning from 11% to 30%.[1]

While the frequency of HABP/VABP in the pediatric population appears lower compared to adults, research has documented incidence rates reaching up to 12% among hospitalized children with pneumonia, with somewhat elevated rates observed in neonates and infants.[2] Nevertheless, these figures may underrepresent the true burden, as establishing a definitive diagnosis can be challenging and the clinical criteria for these conditions vary between adult and pediatric age groups.

Pediatric patients with HABP/VABP caused by multi-drug resistant (MDR) gram-negative organisms face heightened mortality risk and it is a growing challenge in the United States and worldwide. The World Health Organization (WHO) has designated certain pathogens as high-priority threats, including *Acinetobacter baumannii* resistant to carbapenems, Enterobacterales resistant to third-generation cephalosporins, carbapenem-resistant Enterobacterales and carbapenem-resistant *Pseudomonas aeruginosa*.[3] The most common gram-negative pathogens isolated from patients with HABP/VABP include *P. aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Acinetobacter* spp., and *Enterobacter* spp.[4] Resistant mechanisms of these organisms include β-lactamase production, AmpC enzymes, and acquisition of extended-spectrum β-lactamases (ESBL) and carbapenemases, which underscores the importance of newer beta-lactam/beta-

[1] Zilberberg MD, Nathanson BH, Puzniak LA, Shorr AF. Descriptive Epidemiology and Outcomes of Nonventilated Hospital-Acquired, Ventilated Hospital-Acquired, and Ventilator-Associated Bacterial Pneumonia in the United States, 2012-2019. Crit Care Med. 2022 Mar 1;50(3):460-468. doi: 10.1097/CCM.0000000000005298.
[2] Ericson JE, McGuire J, Michaels MG, Schwarz A, Frenck R, Deville JG, Agarwal S, Bressler AM, Gao J, Spears T, Benjamin DK Jr, Smith PB, Bradley JS; 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. 2020 Aug;39(8):658-664. doi: 10.1097/INF.0000000000002642.
[3] "Who Updates List of Drug-Resistant Bacteria Most Threatening to Human Health." World Health Organization, World Health Organization, 17 May 2024, www.who.int/news/item/17-05-2024-who-updates-list-of-drug-resistant-bacteria-most-threatening-to-human-health.
[4] Jiang et al. (2019). Antibiotics for hospital-acquired pneumonia in children. Cochrane Database Syst Rev, Mar 4;2019(3):CD012239.

lactamase inhibitor combinations in treatment.

Children face several clinical risk factors for colonization and infection with MDR bacteria, including premature birth and low birth weight, travel from endemic regions, chronic underlying conditions, frequent and prolonged hospitalizations, exposure to long-term pediatric care settings, immunosuppressive agents, previous antibacterial drug exposure, and presence of indwelling medical devices.[5] Approximately 60% of hospitalized children receive antibacterial drug therapy, which itself contributes to resistance development.[6] In the United States, a notable escalation in antimicrobial resistance among pediatric populations has been observed. From 1999 to 2011, pediatric rates of ESBL-producing organisms rose from 0.28% to 0.92%, while CRE increased from 0% to 0.47%.[7]

To address these MDR infection threats, several new antimicrobial agents have been introduced, including ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, and cefiderocol.[8] At present, only ceftazidime/avibactam and imipenem/cilastatin/relebactam have received pediatric approval for treatment of HABP/VABP in the United States. Additional antibacterial agents are necessary to effectively treat multidrug-resistant pathogens in the pediatric population.

2.2. Analysis of Current Treatment Options

Table 2-1 lists the currently available anti-bacterial agents approved for use in pediatric patients with HABP/VABP.

Table 2-1. Currently Available Treatments for Respiratory Infections in Pediatric Patients

Product Names	Relevant Indication	Approved age range for indication	Important Safety and Tolerability Issues
Cephalosporins			
Cefuroxime sodium	LRTI	≥ 3 months	Use as empiric monotherapy has declined with
Ceftriaxone	LRTI	All ages	
Ceftazidime	LRTI	All ages	

[5] Bassetti M et al. Optimal Management of Complicated Infections in the Pediatric Patient: The Role and Utility of Ceftazidime/Avibactam. Infect Drug Resist. 2020 Jun 12;13:1763-1773.
[6] Venuti F et al. Novel Beta Lactam Antibiotics for the Treatment of Multidrug-Resistant Gram-Negative Infections in Children: A Narrative Review. Microorganisms. 2023 Jul 13;11(7):1798.
[7] Folgori L, Bielicki J. Future Challenges in Pediatric and Neonatal Sepsis: Emerging Pathogens and Antimicrobial Resistance. J Pediatr Intensive Care. 2019 Mar;8(1):17-24. doi: 10.1055/s-0038-1677535.
[8] Chiusaroli L, Tripiciano C, Liberati C, De Pieri M, Brigadoi G, Donà D. Tackling multidrug-resistant Gram-negative infections in children globally: current therapeutic options and perspectives. Expert Opin Pharmacother. 2025 Jul;26(10):1205-1220. doi: 10.1080/14656566.2025.2519690.

Cefepime	Moderate to severe pneumonia	≥ 2 months	emergence of multidrug resistant gram-negative bacilli
Beta-Lactam/Beta-Lactamase Inhibitor Combinations			
Ceftazidime-Avibactam	HABP/VABP	All ages	
Pipercillin-Tazobactam	Nosocomial pneumonia	≥ 2 months	
Carbapenems			
Imipenem-Cilastatin	LRTI	All ages	
Ertapenem	Community acquired pneumonia	≥ 3 months	
Imipenem-Cilastatin-Relebactam	HABP/VABP	Pediatric patients weighing at least 2 kg	
Monobactams			
Aztreonam	LRTI	≥ 9 months	Used in patients with allergy to penicillins or cephalosporins; there are concerns about cross-reactivity with ceftazidime
Aminoglycosides			
Gentamicin sulfate	Serious infections	All ages	Risk of nephrotoxicity and ototoxicity
Tobramycin sulfate	LRTI	All ages	
Amikacin sulfate	Serious infections	All ages	
Other classes			
Colistin	Serious infections	All ages	Risk of nephrotoxicity

Source: Adapted from review of NDA 212819 Supplement 008 dated December 13, 2025 (Table 3).
Abbreviations: LRTI, lower respiratory tract infection; HABP/VABP, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia

The management of HABP/VABP in pediatric patients is complicated by a limited number of available treatment options, a challenge that is particularly pronounced when dealing with MDR infections. In response, some healthcare institutions have developed internal treatment algorithms to guide clinical decision-making. These protocols typically identify cefepime as the initial antibacterial drug of choice, with the option to add concomitant coverage for methicillin-resistant *Staphylococcus aureus* (MRSA) if indicated. For patients with a history of cephalosporin-resistant infection, meropenem is recommended as first-line therapy for HABP/VABP, which is an off-label use across all pediatric age groups.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original NDA 206829 for ZERBAXA (ceftolozane/tazobactam) was approved on December 19, 2014, for the treatment of cUTI including pyelonephritis, and cIAI in combination with metronidazole in patients 18 years or older. On June 3, 2019, a supplemental NDA (S-008) for ZERBAXA was approved for a new indication, for the treatment of HABP/VABP in adult patients aged 18 years and older. The approval letter for the supplement contained a PREA PMR for pediatric assessment (PMR 3637-1: Conduct a safety and pharmacokinetic study in HABP/VABP in children from birth to less than 18 years of age). This efficacy supplement (S-023) was received on November 12, 2025, to address PMR 3637-1 (study P036) and fulfill the requirements of the ZERBAXA Pediatric Written Request (PWR). The supplement proposes to expand the treatment of HABP/VABP to the pediatric population.

3.2. Summary of Presubmission/Submission Regulatory Activity

The key regulatory communications and milestones in the development of ceftolozane/ tazobactam for HABP/VABP are captured below.

The IND application for ZERBAXA was submitted on July 1, 2009, under IND 104490. The Qualified Infectious Disease Product (QIDP) and Fast Track (FT) designations for the treatment of HABP/VABP were granted on February 20, 2013, and April 26, 2013, respectively.

The NDA 206829 for ZERBAXA was approved on December 19, 2014, for the treatment of cUTI including pyelonephritis, and cIAI in combination with metronidazole.

On July 28, 2016, under IND 104490, the Initial Pediatric Study Plan (iPSP) was submitted with a request for a deferral of the pediatric clinical study in order to first establish the safety and efficacy of C/T in the adult population for the treatment of nosocomial pneumonia, which encompasses HABP/VABP. After several iterations of comments, the Agency issued the Agreed Initial Pediatric Study Plan – Agreement letter on May 12, 2017.

On March 7, 2018, a proposed pediatric study request (PPSR) was first submitted to the NDA application. The proposed study was for a randomized, active comparator-controlled, multi-center, double-blind clinical trial to study the safety and efficacy of C/T versus standard of care antibiotics for the treatment of acute pulmonary exacerbations in pediatric participants with cystic fibrosis. On June 1, 2018, the Agency denied issuing a Written Request (WR) for the proposed pediatric study due to deficiencies in study design. The Applicant resubmitted the PPSR on October 14, 2021, with a revised pediatric study proposal to conduct a study evaluating safety, tolerability and pharmacokinetics of C/T in pediatric participants with nosocomial pneumonia.

On December 3, 2018, the Applicant submitted a prior approval supplement (PAS) for a new indication, for the treatment of HABP/VABP, and on June 3, 2019, the sNDA was approved for the treatment of HABP/VABP in adult patients aged 18 years and older. Concurrent with this approval, the Agency issued PREA PMR 3637-1 to "Conduct a safety and pharmacokinetic study in HABP/VABP in children from birth to less than 18 years of age."

On February 8, 2022, the Agency issued a PWR containing a proposed pediatric study request for C/T in the treatment of nosocomial pneumonia (HABP/VABP) in pediatric patients from birth to less than 18 years of age. The PWR included a request to conduct the following study: "An open-label, non-comparative, multi-center study to evaluate the safety, tolerability, and pharmacokinetics of C/T in pediatric participants from birth (>32 weeks gestational age and ≥ 7 days postnatal) to <18 years of age with nosocomial pneumonia." The Applicant accepted the PWR for pediatric studies on June 17, 2022.

The PWR was amended on September 8, 2023, to extend the due date from November 30, 2023, to June 30, 2026, due to delays related to the global recall of ZERBAXA in December 2020, loss of study sites due to international conflict, and the COVID-19 pandemic. The study included in the PWR was also required to be conducted under PREA.

The Applicant submitted Supplement 023 on November 11, 2025, to provide for the final study report to fulfill PREA PMR 3637-1 and the requirements of the PWR. The supplement proposes the addition of pediatric patients from birth up to 18 years of age to the treatment of HABP/VABP. Supplement 023 has been granted a priority review and has a Prescription Drug User Fee Act (PDUFA) action goal date of May 12, 2026.

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

4.1. Office of Scientific Investigations (OSI)

In this supplement, the number of patients enrolled at each site was small and there were no concerning findings regarding safety or efficacy identified at any particular site. As a result, it was determined that no clinical site inspections were necessary for this supplement. On December 12, 2025, the clinical pharmacology reviewer requested a routine biopharmaceutical inspection of (b) (4) and (b) (4)., by the Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS).

The OSIS arranged a clinical inspection of study site of Iolanda Jordan Garcia at Hospital Universitario Sant Joan de Déu, Barcelona, Catalonia, Spain. Form FDA 483 was not issued at the inspection close-out. There was one discussion item regarding adverse events that were not entered into the electronic data capture (EDC) contemporaneously. However, after reviewing

the inspectional findings and exhibits provided in the Establishment Inspection Report (EIR), there are no concerns regarding the reliability of the data and human subject protection for inspected study P036MK7625A. OSIS determined that an inspection is not needed for (b) (4) since OSIS has conducted an inspection for the same site under another NDA.

4.2. Product Quality

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use, but the expected introduction concentration (EIC) of the substance at the point of entry into the aquatic environment is <1 ppb. Based on the product, its indications, and its dosing, the use amount is expected to be substantially lower than 1 ppb. Extraordinary circumstances are not indicated, in accordance with 21 CFR 25.15, and the required statement on extraordinary circumstances also was provided. Therefore, the claim for an exclusion from an EA is acceptable.

4.3. Clinical Microbiology

From a clinical microbiology perspective, the Applicant has provided adequate in vitro and in vivo data to support the approval of ZERBAXA (ceftolozane/tazobactam) for the treatment of HABP and VABP in the specified pediatric population. This determination is supported by data from the original NDA submission for HABP/VABP in adults, as well as evidence indicating the causative bacterial pathogens are comparable between adult and pediatric populations. Additional supporting details are available in the clinical and clinical pharmacology review document.

No new clinical microbiology studies were conducted as part of this supplement, and no efficacy endpoints were included in the pediatric study P036. However, the Applicant submitted the in vitro susceptibility data for C/T against respiratory tract infection (RTI) pathogens isolated from pediatric patients in the United States. These data were derived from the ongoing global SMART surveillance program (2019-2023) from gram-negative bacilli.

Key findings are summarized below:

- Among 4,650 U.S. RTI isolates of Enterobacterales, the overall MIC90 was 2 mcg/mL. Stratified analyses demonstrated an MIC90 of 1 mcg/mL for 566 pediatric isolates and 4 mcg/mL for 4,024 adult isolates.
- Among 2,624 U.S. RTI isolates of *Pseudomonas aeruginosa*, the overall MIC90 was 4 mcg/mL. For the subset of 266 pediatric isolates, the MIC90 was 2 mcg/mL, compared to 4 mcg/mL for 2,318 adult isolates.

Collectively, these data support the microbiological activity of C/T against relevant RTI pathogens in pediatric patients and are consistent with findings observed in adult populations.

5 Nonclinical Pharmacology/Toxicology

No new nonclinical safety studies were conducted to support this supplement, and no new nonclinical data were submitted in this supplement. Refer to the Pharmacology/Toxicology Review supporting the original NDA approval (dated 12/19/2014) for additional information.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology information contained within the current sNDA supports the approval of ZERBAXA (C/T) for the treatment of HABP/VABP in pediatric patients from birth (defined as at least 32 weeks GA and at least 7 days postnatal age) to <18 years of age. The clinical pharmacology program included 1) PK data from a multi-dose phase 1 study (Study P036) in pediatric patients with HABP/VABP, 2) population PK modeling and simulation analyses integrating data from four pediatric clinical studies, and 3) probability of target attainment (PTA) analyses using nonclinical pharmacokinetic-pharmacodynamic (PK-PD) targets.

The dosage recommended by the review team differs from the Applicant's original proposal and was primarily based on the exposure (AUC_{0-8} and Cmax) matching between pediatric and adult HABP/VABP patients. Additional support for the recommended dosage was the projected joint epithelial lining fluid (ELF) PTA of ≥ 90% at the susceptibility breakpoint MICs. The exposure matching and PTA findings did not support the Applicant's originally proposed dosage of 60 mg/kg (ceftolozane 40 mg/kg and tazobactam 20 mg/kg) administered as a 1-hour infusion for pediatric patients 2 to <18 years of age. Therefore, the review team recommended a 25% higher dose of 75 mg/kg (ceftolozane 50 mg/kg and tazobactam 25 mg/kg) administered as a 2-hour infusion for patients 2 to <18 years. The Applicant's originally proposed dosage was deemed acceptable for patients from birth to <2 years of age, as exposures in this age group were within or close to the adult reference range and joint ELF PTAs exceeded 90% at the susceptibility breakpoint. The Applicant agreed with the recommended 25% higher dose for pediatrics ≥2 years; however, proposed an identical infusion time of 2 hours across all pediatric dosing recommendations to mitigate the potential for confusion and medication errors. The Applicant's proposal is reasonable from a clinical pharmacology perspective. See **Table 6-1** for the finally agreed upon dosage recommendations.

For pediatric patients 2 to <18 years with eGFR 15 to 50 mL/min/1.73m², the review team recommends dosages 25% higher than those proposed by the Applicant. The review team also recommends extending infusion duration to 2-hour for this age group. For eGFR <15 mL/min/1.73m^2 on intermittent hemodialysis (IHD), the Applicant's proposed dosage was reasonable; however, the review team recommends that infusion time be extended to 2 hours for dosage instruction harmonization. A dosage was not established for pediatric patients with eGFR <15 mL/min/1.73m^2 not receiving IHD. These recommendations are detailed in **Table 6-2** as well as in the Comprehensive Clinical Pharmacology Review in **Section 6.2**.

Additionally, this submission included proposed C/T dosages for pediatric patients 2 to <18 years with cUTI and cIAI and with eGFR ≤50 ml/min/1.73m^2 (**Table 6-3**). The submitted information was reviewed, and the proposed C/T dosages were found to be adequately supported. Similar to HABP/VABP, a dosage was not established for pediatric patients with eGFR <15 mL/min/1.73m^2 not receiving IHD. For pediatric patients less than 2 years of age with renal impairment, dosage is not established.

Table 6-1. Applicant's Originally Proposed and Agreed Upon ZERBAXA (C/T) Dosage in Pediatric Patients with HABP/VABP#

Age Range	Applicant's Original Proposal		Agreed Upon Recommendations	
	Dosage¶	IV Infusion Time	Dosage¶	IV Infusion Time
12 to <18 y	60 mg/kg (max 3 g) every 8 hours	1 hour	75 mg/kg (max 3g) every 8 hours	2 hours
7 to <12y				
2 to <7y				
3 mo to <2y			60 mg/kg every 8 hours	
Birth† to <3 m				

Source: Clinical Pharmacology Reviewer
eGFR > 50 mL/min/1.73 m² for patients ≥2 years only;
† Birth defined as >32 weeks gestational age and at least 7 days postnatal age.
¶ Note on Maximum Dose: the weight at which the maximum dose of 3g is reached differs between the proposed and recommended regimens. The Applicant's proposed 60 mg/kg dose reaches the 3 g cap at a body weight of 50 kg. The Review Team's recommended 75 mg/kg dose reaches the 3g cap at a body weight of 40 kg.
Abbreviations: mo- month, y- year,

Table 6-2. FDA Recommended and Applicant Proposed ZERBAXA (C/T) Dosage in Pediatric Patients 2 to <18 Years with HABP/VABP and eGFR 50 ml/min/1.73m² or Less

eGFR (ml/min/1.73 m²)	Applicant's Original Proposal		FDA Recommendations	
	Dosage	IV Infusion Time	Dosage	IV Infusion Time
30 to 50	(b) (4) mg/kg (max 1.5 g) every 8 hours	1 hour	37.5 mg/kg (max 1.5 g) every 8 hours	2 hours
15 to <30	(b) (4) mg/kg (max 0.75 g) every 8 hours		18.75 mg/kg (max 0.75 g) every 8 hours	
Receiving IHD	LD: 45 mg/kg (max 2.25 g) MD: 9 mg/kg (0.45 g) every 8 hours†		LD: 45 mg/kg (max 2.25 g) MD: 9 mg/kg (0.45 g) every 8 hours†	

Source: Clinical Pharmacology Reviewer
¶ Maximum Dose: the weight at which the maximum doses reached differs between the proposed and recommended regimens. The Applicant's proposed max dose cap is at a body weight of 50 kg. The Review Team's recommended max dose cap is at a body weight of 40 kg.
†Maintenance dose received on IHD days at the earliest possible time post-completion of IHD. Abbreviations: IHD, intermittent hemodialysis; LD, loading dose; MD, maintenance dose.

Table 6-3. Recommended ZERBAXA (C/T) Dosage in Pediatric Patients 2 to <18 Years with cUTI/cIAI and eGFR 50 ml/min/1.73m^2 or Less

eGFR (ml/min/1.73 m^2)	ZERBAXA Dosage¶	Infusion Time
30 to 50	15 mg/kg (max 0.75 g) every 8 hours	1 hour
15 to <30	7.5 mg/kg (max 0.375 g) every 8 hours	
Receiving IHD	LD: 15 mg/kg (max 0.75 g) MD: 3 mg/kg (max 0.15 g) every 8 hours†	

Source: Clinical Pharmacology Reviewer
¶ Pediatric patients with cUTI or cIAI and renal impairment weight greater than 50 kg will receive the recommended cUTI/cIAI dose for adults with renal impairment.
† Maintenance dose received on IHD days at the earliest possible time post-completion of IHD
Abbreviations: IHD, intermittent hemodialysis -; LD-loading dose ; MD-maintenance dose

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 recommended C/T dosage (**Table 6-1, Table 6-2, and Table 6-3**) for the treatment of HABP/VABP in pediatric patients from birth (>32 weeks GA and at least 7 days postnatal age) to <18 years of age.

The clinical pharmacology program is comprised of: (1) a phase 1, open-label, non-comparative study (P036) evaluating the safety, tolerability, and PK of C/T in pediatric patients from birth to <18 years of age with confirmed or suspected HABP/VABP; (2) population PK analyses integrating data from four pediatric clinical studies (P010, P034, P035, and P036); and (3) joint PTA analyses in plasma and ELF. Collectively, the clinical pharmacology program supports extrapolation of effectiveness of C/T from adult HABP/VABP patients to pediatric patients. This extrapolation is based on C/T exposure matching between (a) HABP/VABP pediatric patients from birth to <18 years of age receiving the recommended C/T dosage (**Table 6-1**) and (b) adult HABP/VABP patients receiving the currently approved C/T dosage. This exposure comparison based extrapolation approach is appropriate given the similar disease pathophysiology, causative gram-negative bacterial pathogens, and expected similar treatment response between adult and pediatric HABP/VABP patients. In addition, the Applicant conducted joint PTA analyses, especially using the ELF PK-PD target, which provided supportive evidence. The key findings from exposure comparison and joint PTA supporting the recommended dosage are summarized under the next question. See **Section 15.2.1** for additional details on Study P036, **Section 15.2.3** for population PK analyses, and **Section 15.2.2** for PTA analyses.

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

The Applicant's originally proposed ZERBAXA dosage of 60 mg/kg (ceftolozane 40 mg/kg + tazobactam 20 mg/kg) every 8 hours as a 1-hour infusion was adequately supported for pediatric HABP/VABP patients <2 years of age. However, the proposed dosage was not adequately supported for pediatric patients 2 to <18 years of age due to observed lower exposures compared to the adult HABP/VABP patients. Therefore, the review team recommended 75 mg/kg (ceftolozane 50 mg/kg + tazobactam 25 mg/kg) every 8 hours infused over 2 hours for patients 2 to <18 years. The Applicant proposed to maintain an identical infusion time of 2 hours across all pediatric dosing recommendations to mitigate the potential for confusion and medication errors. The Applicant's proposal is reasonable from a clinical pharmacology perspective. The following is a summary of assessments of the proposed dosage across different pediatric groups.

Dosage for Pediatric Patients <2 Years

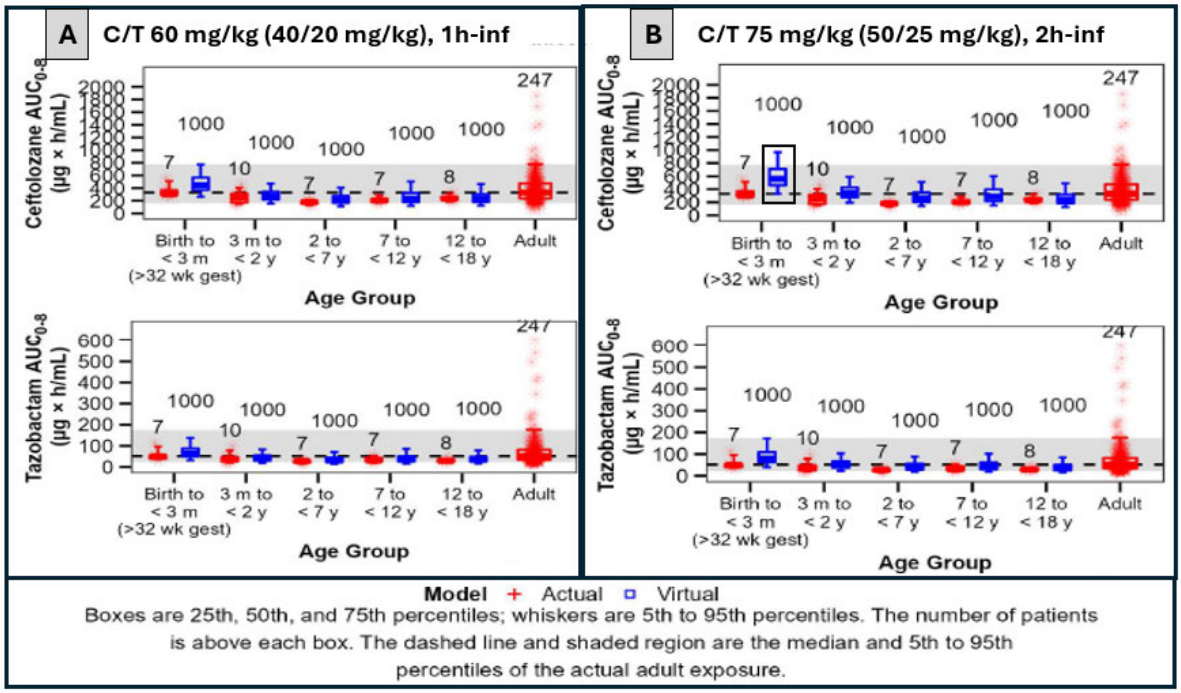
The Applicant's originally proposed 60 mg/kg 1-hour infusion regimen is adequately supported for patients <2 years of age based on: (1) Comparable AUC_{0-8} values between the virtual pediatric population and the adult reference population (**Figure 6-1** and **Table 6-4**) and (2) ≥ 90% PTA at up to C/T MIC of 4 µg/mL (**Table 6-5**). However, subsequently the Applicant proposed 2 hours infusion duration in this age group to further harmonize the dosing instructions with other age groups (see below). The Applicant's proposal is reasonable from a clinical pharmacology perspective since extending the infusion from 1 hour to 2 hours in pediatrics <2 years of age is not expected to increase C/T AUC_{0-8}. The proposal will reduce Cmax, however, the decrease in Cmax is not expected to have an impact on effectiveness given that C/T antibacterial activity is not reported to be associated with Cmax. Instead, the C/T antibacterial activity is associated with the percentage of dosing interval that the free (unbound) ceftolozane and tazobactam drug concentration remains above the MIC and a threshold concentration, respectively.

Dosage for Pediatric Patients ≥2 Years with eGFR >50 mL/min/1.73m^2

Effectiveness Considerations

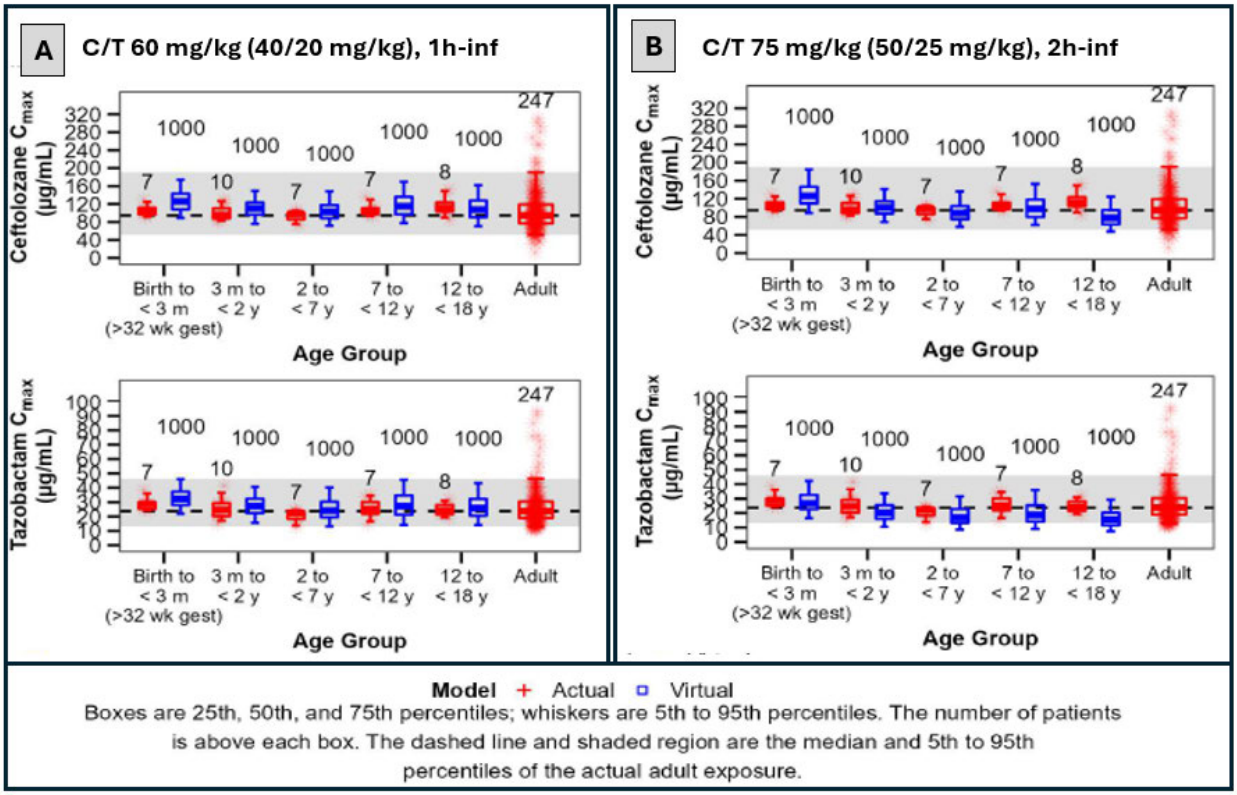
The Applicant's proposed 60 mg/kg 1-hour infusion regimen was not adequately supported for patients 2 to <18 years based on the following effectiveness related concerns: (1) up to ≥~20% of the virtual pediatric population had AUC_{0-8} values below the 5th percentile of the adult reference population (**Table 6-4**); (2) adult median post hoc ceftolozane and tazobactam AUC_{0-8} exposures were 1.6- and 1.8-fold higher, respectively, than in pediatric patients ≥2 years (**Table 15-1, Figure 6-1**); and (3) joint ELF PTA did not meet the ≥90% threshold at the susceptibility breakpoint C/T MIC of 4 µg/mL (**Table 6-5** and **Section 15.2.2**). See **Section 15.2.2** for additional details. With the review team recommended dosage of 75 mg/kg (50/25 mg/kg C/T via 2-hour Infusion, <10-12% of the virtual pediatric population is projected to have AUC_{0-8} values below the 5th percentile of the adult reference population in the 2 to <12 years age group. For the 12 to <18 years group, exposure improvement with 75 mg/kg was minimal (**Table 6-4** and **Figure 6-1**)— as expected given patients ≥40 kg receive the adult fixed dose of 3 g. With respect to PTAs, joint ELF PTAs improved to >90% (**Table 6-5**)**.** In an effort to harmonize dosage instructions and reduce potential for medication errors across the 2 to <18 years age range, the review team recommended 2-hour infusion across the age range of 2-18 years.

Figure 6-1. C/T Plasma AUC_{0-8},ss for Post Hoc and Virtual Pediatric HABP/VABP Patients on 60 mg/kg 1-Hour Infusion (A) or 75 mg/kg 2-Hour Infusion (B), Compared to Adult HABP/VABP Patients from Study P008 (CrCL >50 mL/min)



Source: Adapted from Figures 1 and 5 in clinical-information-amendment-08apr2026.pdf
Note: Black box = the AUC values for birth to <3 month on the C/T 75 mg/kg q8h, 2h infusion dosage are projected to exceed the 95th percentile of adult reference population.

Figure 6-2. C/T Plasma Cmax,ss for Post Hoc and Virtual Pediatric HABP/VABP Patients on 60 mg/kg 1-Hour Infusion (A) or 75 mg/kg 2-Hour Infusion (B), Compared to Adult HABP/VABP Patients from Study P008 (CrCL >50 mL/min)



Source: Adapted from Figures 1 and 5 in clinical-information-amendment-08apr2026.pdf

Table 6-4. Proportion of Virtual Pediatric HABP/VABP Patients (n=1000) with AUC_{0-8} Below, Within, or Above the Adult Reference Range (Study P008, CrCL >50 mL/min, n=247) by Age Group: 60 mg/kg 1-Hour Infusion vs. 75 mg/kg 2-Hour Infusion

Drug	Relative to Adult Prediction Interval	Original Dosage 60 mg/kg q 8h (1h infusion)					Recommended Dosage 75 mg/kg q 8h (2h infusion)				
		Birth to <3m	3m to <2y	2 to <7y	7 to <12y	12 to <18y	Birth to <3m	3m to <2y	2 to <7y	7 to <12y	12 to <18y
		Percentage					Percentage				
Ceftolozane AUC_{0-8}	Below	0.2	5.9	23.6	18.4	17.7	0.0	1.2	9.7	7.5	16.8
	Within	95.0	93.9	76.4	81.1	81.8	81.5	98.3	90.1	90.8	82.5
	Above	4.8	0.2	0.0	0.5	0.5	18.5	0.5	0.2	1.7	0.7
Tazobactam AUC_{0-8}	Below	1.0	11.0	23.9	20.2	19.8	0.4	4.6	11.5	10.5	18.7
	Within	97.9	88.9	76.1	79.7	80.1	95.4	95.2	88.4	89.3	81.2
	Above	1.1	0.1	0.0	0.1	0.1	4.2	0.2	0.1	0.2	0.1

Source: Adapted from Tables 2 and 8 in clinical-information-amendment-08apr2026.pdf

Red-shaded cells (≥20%), Yellow shaded cells (≥10%-19.9%), Green shaded cells- (<10%)

Table 6-5. Steady-State Joint ELF PTA at Susceptibility Breakpoint MICs for Pediatric HABP/VABP Patients: 60 mg/kg 1-Hour Infusion vs. 75 mg/kg 2-Hour Infusion

Dosage	C/T MIC¶ (µg/mL)	Joint ELF PTA ≥90% (Ceftolozane:40% fT>MIC# and Tazobactam: 20% fT>CT=1¥ µg/mL)†				
		Birth to <3m	3m to <2y	2 to <7y	7 to <12y	12 to <18y
Original Dosage (60 mg/kg q8h, 1h infusion)	2	Yes	Yes	No (83%)	No (86%)	No (86%)
	4	Yes	Yes	No (83%)	No (86%)	No (86%)
Recommended Dosage (75 mg/kg q8h, 2h infusion)	2	Yes	Yes	Yes	Yes	Yes
	4	Yes	Yes	Yes	Yes	Yes

Source: Adapted from Tables 3 and 9 in clinical-information-amendment-08apr2026.pdf
¶Susceptibility Breakpoint for Enterobacterales (C/T MIC = 2 µg/mL) and *P. aeruginosa* (C/T MIC = 4 µg/mL)
#%fT>MIC=Percentage of dosing interval that the free (unbound) drug concentration remains above the minimum inhibitory concentration
¥Percentage of dosing interval that the free (unbound) drug concentration remains above threshold concentration
†Yes is PTAs ≥ 90%; No is PTA <90% (actual PTA)

The Applicant proposed that the 60 mg/kg dose was appropriate for all pediatric age groups provided the (b) (4) is used as the comparator. The review team does not agree with this approach because the safe and effective exposure range was derived from a phase 3 study in which the majority of patients (~75%) were older than (b) (4) years.

The Applicant also proposed (b) (4) The review team does not agree with this proposal given: (1) the proposal of (b) (4) would not address the concern of lower AUCs in comparison to the adult reference population, i.e., the primary basis of extrapolation, and (2) for pediatric HABP/VABP patients efficacy data are not available to ascertain (b) (4) are adequate to support an extrapolation of effectiveness.

Safety Considerations

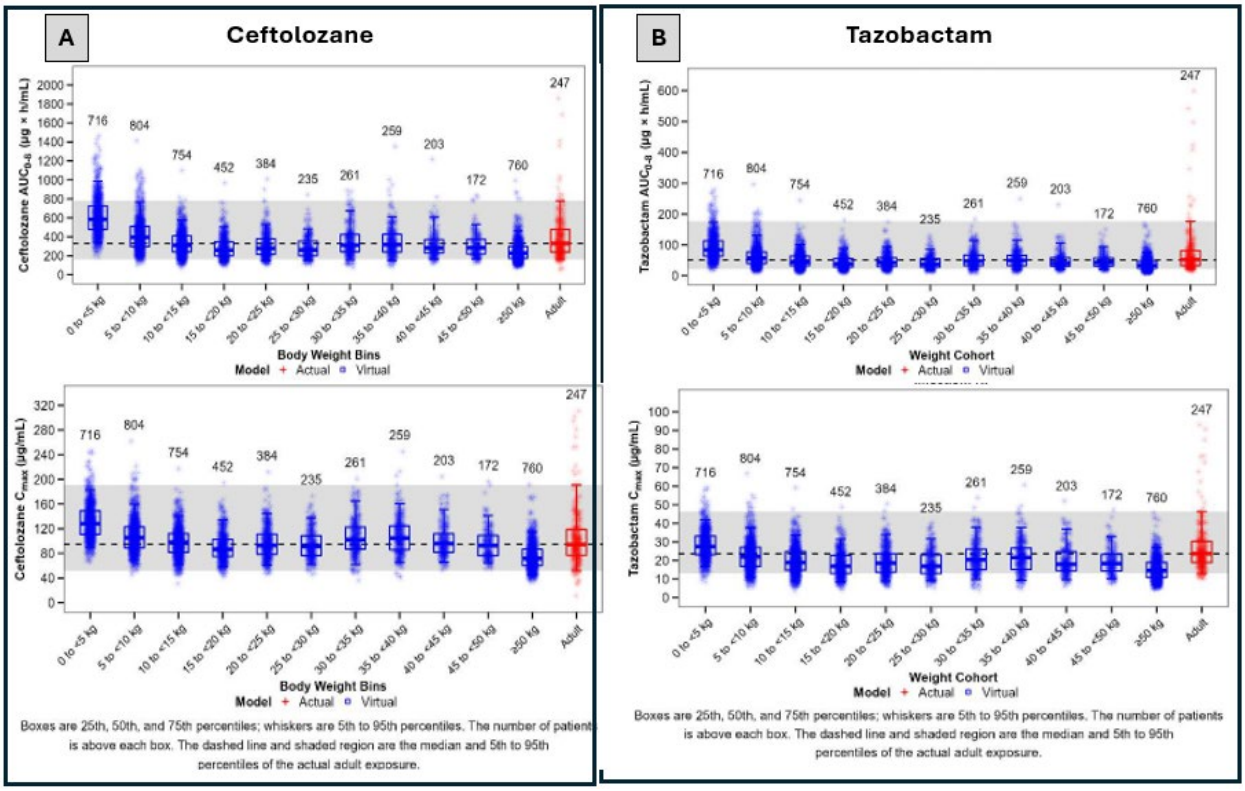
The review team also considered potential safety implications of recommended 25% higher dose for the pediatric ≥2 years of age than the dose evaluated in Study P036. The 2-hour infusion reduces Cmax relative to a 1-hour infusion and the projected Cmax is expected to be lower than the reference adult Cmax estimates (**Figure 6-2**). With respect to projected AUC estimates, the 75 mg/kg dose did not pose any increased potential safety risk in any of the age groups except for the birth to <3 months age group. In the birth to <3 months group, the ceftolozane AUC estimates were projected to exceed the adult 95th percentile AUC_{0-8} in ~19% of virtual patients (**Table 6-4**). For the 3 months to <2 year group, no significant differences in exposure comparison findings noted for either dosage (**Table 6-4**). Based on these collective

safety considerations, the review team did not recommend a 25% dose increase in the birth to <2 year age range.

Fixed Dosage for Pediatric Patients ≥40 kg with eGFR >50 mL/min/1.73m²

The Applicant proposed 60 mg/kg C/T dosage with capping the maximum dose at the adult fixed C/T dose of 3 g (ceftolozane 2 g + tazobactam 1 g) with 1 hour infusion. The review team agrees with the proposed maximum dose, however, recommends a 2-hour infusion duration rather than the proposed 1-hour infusion. The 2-hour infusion duration is for the purpose of harmonization with other pediatric age groups. It is noteworthy that with the review team recommended C/T dose of 75 mg/kg, the adult maximum dose of 3 g is reached at ≥40 kg weight (instead of the previous weight threshold at ≥50 kg). Exposure comparison findings across the body weight groups support the proposed dose capping strategy with the recommended C/T dosage of 75 mg/kg q8h (**Figure 6-3**). The recommended dosage with a 2-hour infusion produced AUC_{0-8} and Cmax values for both drugs that were generally comparable to the adult reference range (**Figure 6-3**).

Figure 6-3. C/T AUC_{0-8}ss and Cmax,ss by Weight Group in Virtual Pediatric HABP/VABP Patients on 75 mg/kg 2-Hour Infusion, Compared to Adult HABP/VABP Patients from Study P008 (CrCL > 50 mL/min)



Source: Adapted from Figure 6 in clinical-information-amendment-08apr2026.pdf

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

Yes, C/T dosage adjustments are required for patients with eGFR 15 to 50 mL/min/1.73m². The final agreed upon dosage adjustments for pediatric patients 2 years of age and older are provided in **Table 6-2**.

The Applicant has not proposed C/T dosage adjustment recommendations for patients <2 years of age with renal impairment. In this age group, renal clearance is driven by renal maturation rather than physiological renal impairment. Therefore, it is not possible to reliably characterize the impact of varying degrees of renal impairment on C/T pharmacokinetics to derive appropriate dosage adjustments. Due to this limitation, the Applicant's proposal to limit renal impairment dosage adjustment for pediatric patients ≥ 2 years of age is reasonable.

For pediatric patients aged 2 to <18 years, the eGFR-drug clearance relationship established in adults was incorporated into the pediatric population PK model, assuming the proportional effect of renal impairment on drug clearance is equivalent between adults and pediatric patients ≥2 years of age. Using the population model, the Applicant proposed dosage adjustment for HABP/VABP, cUTI, and cIAI indications as discussion below.

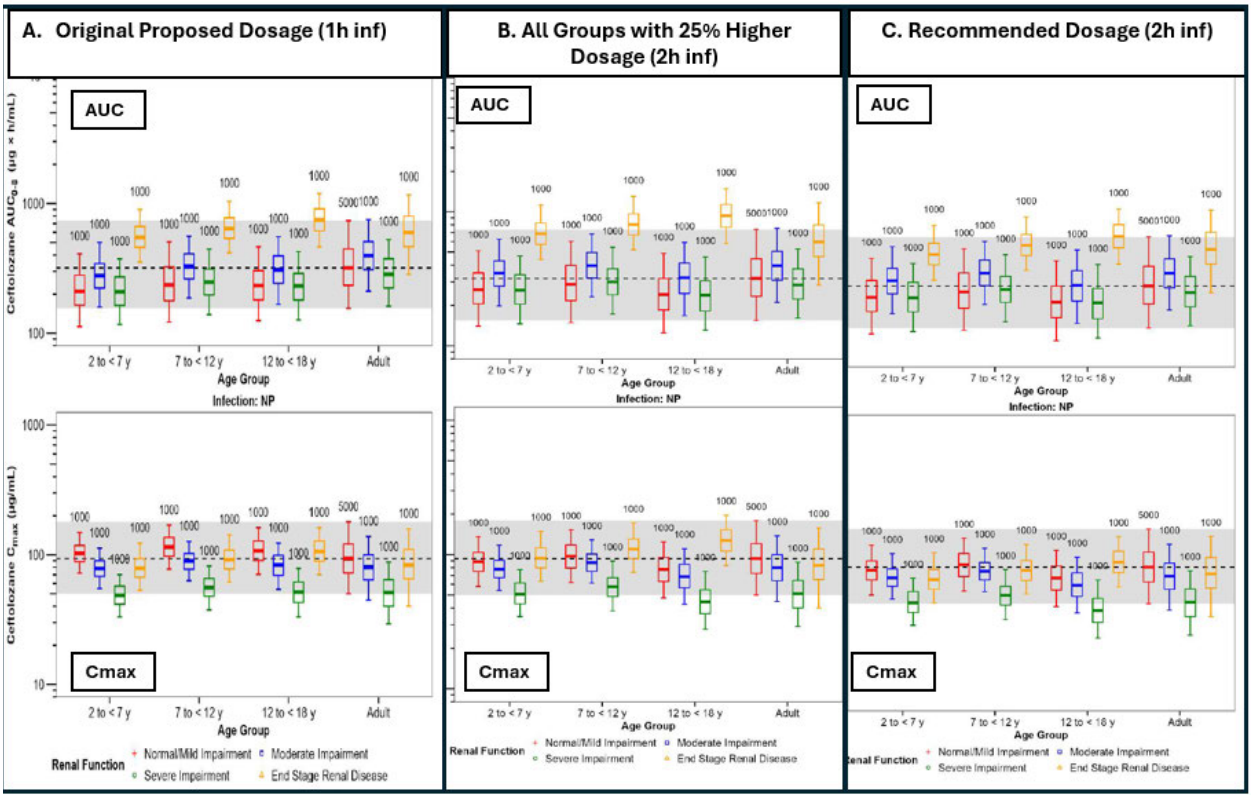
HABP/VABP

For HABP/VABP, the Applicant's proposed dosages for renally impaired patients, which were proportional reductions from the proposed 60 mg/kg dose, resulted in C/T AUC_{0-8} values substantially lower than the adult HABP/VABP reference population and were not accepted by the Review Team (**Figure 6-4A and Figure 6-5A**). Similar to the recommendation for pediatric patients with normal renal function, the review team recommended dosages 25% higher than those proposed by the Applicant, administered as a 2-hour infusion, for patients with eGFR 15 to 50 mL/min/1.73m² **(Figure 6-4B and Figure 6-5B)**. The 25% higher dose with 2-hour infusion improved ceftolozane AUC_{0-8} alignment with the adult median for patients 2 to <12 years across both eGFR categories; for patients 12 to <18 years, exposure improvement was minimal but the adjustment was retained for harmonization across the 2 to <18 years age range. Joint ELF PTAs ≥ 90% were achieved at the susceptibility breakpoint MICs for all renal impairment categories and age groups with the recommended dosages (**Table 6-6**).

For patients with eGFR <15 mL/min/1.73m² on IHD, the originally proposed C/T loading dose of 30/15 mg/kg (ZERBAXA 45 mg/kg) and maintenance dose of 6/3 mg/kg (ZERBAXA 9 mg/kg) q8h was accepted. The infusion time was recommended to be extended to 2 hours for harmonization. The proportionally higher dose (b) (4)) was not recommended because ceftolozane exposures would substantially exceed the adult HABP/VABP reference population (**Figure 6-4B**) without meaningful PTA improvement, with joint ELF PTAs approaching 100% at MICs up to 8 µg/mL with the originally proposed dosage (**Table 6-6**).

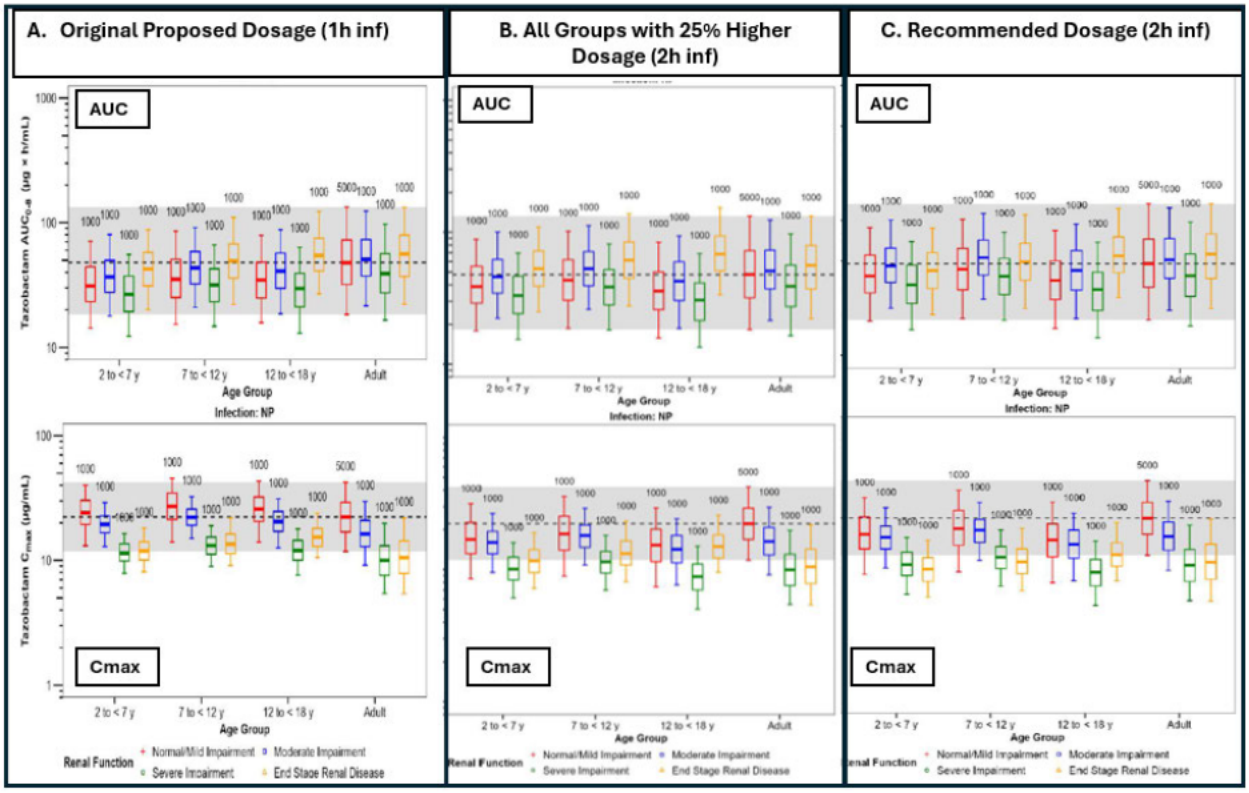
Figure 6-4. Ceftolozane Plasma AUC0-8,ss and Cmax,ss in Virtual Pediatric HABP/VABP Patients 2 to <18 Years with eGFR ≤50 mL/min/1.73m²: Original Proposed Dosage (A), 25%

Higher Dosage (B), and Recommended Dosage (C), Compared to Adult Virtual HABP/VABP Patients by Renal Function Category



Source: Adapted from Figures 3, 7, and 9 in clinical-information-amendment-08apr2026.pdf
Note: end-stage renal disease (0 to <15 ml/min/1.73m^2 on intermittent hemodialysis) recommended dosage has the same dose level as the original proposed dosage but with a 2h infusion
Boxes are 25th, 50th, 75th percentiles; whiskers are 5th to 95th percentiles. Symbols show data points outside this range. The number of patients is above each box. The dashed line and shaded region are the median and 5th to 95th percentiles of the adult, normal renal function exposure.

Figure 6-5. Tazobactam Plasma AUC0-8,ss and Cmax,ss in Virtual Pediatric HABP/VABP Patients 2 to <18 Years with eGFR ≤50 mL/min/1.73m²: Original Proposed Dosage (A), 25% Higher Dosage (B), and Recommended Dosage (C), Compared to Adult Virtual HABP/VABP Patients by Renal Function Category



Source: Adapted from Figures 4, 8, and 10 in clinical-information-amendment-08apr2026.pdf
Note: end-stage renal disease (0 to <15 ml/min/1.73m² on intermittent hemodialysis) recommended dosage has the same dose level as the original proposed dosage but with a 2h infusion
Boxes are 25th, 50th, 75th percentiles; whiskers are 5th to 95th percentiles. Symbols show data points outside this range. The number of patients is above each box. The dashed line and shaded region are the median and 5th to 95th percentiles of the adult, normal renal function exposure.

Table 6-6. Steady-State Joint ELF PTA at the *P. aeruginosa* Breakpoint (MIC = 4 µg/mL) in Virtual Pediatric HABP/VABP Patients with eGFR ≤ 50 mL/min/1.73m²

Dosage	eGFR (ml/min/1.73m²)	2 to <7 y	7 to <12 y	12 to <18y
Original Proposed Dosage				
(b) (4) mg/kg q8h (1h inf)	30 to 50	99%	99%	99%
(b) (4) mg/kg q8h (1h inf)	15 to <30	99%	99%	99%
LD 45 mg/kg x 1 (1h inf) MD 9 mg/kg q8h (1h inf)	Receiving IHD	100%	100%	100%
Recommended Dosage				

37.5 mg/kg q8h (2h inf)	30 to 50	100%	100%	100%
18.75 mg/kg q8h (2h inf)	15 to <30	100%	100%	100%
LD 45 mg/kg x 1 (2h inf) MD 9 mg/kg q8h (2h inf)†	Receiving IHD	100%	100%	100%

Source: Adapted from Tables 3, 4, 5, 14, and 16 in clinical-information-amendment-20mar2026.pdf
Note: PK-PD target for ceftolozane is 40%fT>MIC and tazobactam is 20%fT>MIC.
† PTA analyses for this dosage at 2 hour infusion were not provided in the submission. Based on time-dependent PK-PD of C/T, extending the infusion from 1 to 2 hours at the same dosage extends the duration free unbound drug concentration remains above MIC without altering the AUC. Since joint ELF PTA for same dose as 1-hour infusion has 100% PTA, then joint PTA for 2-hour infusion will remain the same.
LD= Loading dose, MD= Maintenance dose, IHD- intermittent hemodialysis, INF- infusion, h- hour

cUTI/cIAI

The original pediatric cUTI/cIAI dosage was supported by exposure comparison with adults, joint plasma PTAs, and phase 2 clinical efficacy data (P034 and P035). The proposed renal impairment dosages are primarily based on extrapolation of the adult eGFR-drug clearance relationship to the pediatric population. These dosages represent proportional reductions from the approved 30 mg/kg pediatric dose, consistent with the approach applied to HABP/VABP renal impairment dosing. For patients with eGFR <15 mL/min/1.73m^2 on IHD, the cUTI/cIAI loading dose represents one-half of the normal renal function dose, compared to three-fourths for HABP/VABP, reflecting different PK behavior during IHD at each dose level.

The proposed dosages are supported by the following considerations. As shown in **Table 6-7,** simulated C/T AUC_{0-8} values in pediatric cUTI and cIAI patients with eGFR ≤50 ml/min/1.73m^2 receiving the recommended adjusted dosages (based on renal function) were lower than adult cUTI and cIAI virtual patients with CrCL >50 ml/min. However, despite these lower C/T exposures relative to adults, the dose-adjusted C/T AUC_{0-8} values in pediatric patients with eGFR ≤50 mL/min/1.73m^2 were comparable or higher than those in pediatric patients with eGFR >50 mL/min/1.73m^2 receiving the approved dosage evaluated in phase 2 studies- P034 and P035 (**Table 6-8**), supporting effectiveness. These higher exposures seen in **Table 6-8** are consistent with the higher joint plasma PTAs observed in pediatric patients with eGFR ≤50 ml/min/1.73m^2 compared to pediatric patients with eGFR >50 ml/min/1.73m^2, as discussed below.

Individual ceftolozane PTAs at the *P. aeruginosa* breakpoint (MIC = 4 µg/mL) were ≥90% across all renal impaired subgroups with eGFR ≤50 ml/min/1.73m^2 for both cUTI and cIAI. However, joint PTAs did not uniformly meet the 90% threshold (**Table 15-3 and Table 15-4**). For context, joint PTAs for patients with eGFR >50 mL/min/1.73m^2 are also shown in **Table 15-3 and Table 15-4** and are substantially lower (50–65%) than the >85% joint PTAs reported in the 2022 pediatric cUTI/cIAI approval,[9] likely reflecting lower predicted tazobactam exposures from the updated tazobactam population PK model. This PTA drop is not considered an effectiveness concern given the individual ceftolozane PTAs across all patients with eGFR ≤50

[9] NDA206829-Suppl 11. Unireview; DARRTS date 4/20/2022

mL/min/1.73m^2. See **Section 15.2.2** for additional details on tazobactam exposures effect on joint PTAs.

Table 6-7. Median C/T AUC_{0-8} in Virtual Pediatric cUTI and cIAI Patients 2 to <18 Years Relative to Adult Virtual Reference Population (CrCL >50 ml/min) by Renal Function Category (Fold Difference)

Infection	Drug	eGFR (mL/min/1.73m^2	2 to <6y	6 to <12y	12 to <18y
cUTI	Ceftolozane	30 to 50	0.71	0.80	0.79
		15 to <30	0.54	0.63	0.60
		Receiving IHD	1.02	1.21	1.42
	Tazobactam	30 to 50	0.66	0.72	0.73
		15 to <30	0.47	0.56	0.52
		Receiving IHD	0.50	0.57	0.65
cIAI	Ceftolozane	30 to 50	0.71	0.80	0.79
		15 to <30	0.54	0.63	0.61
		Receiving IHD	1.04	1.23	1.46
	Tazobactam	30 to 50	0.66	0.72	0.73
		15 to <30	0.47	0.56	0.52
		Receiving IHD	0.50	0.57	0.65

Source: Adapted from Report 08wwfz.pdf-Tables 44-51
Abbreviations: cUTI- complicated urinary tract infections, cIAI- complicated intra-abdominal infection, y- year, IHD- intermittent hemodialysis, eGFR- estimated glomerular filtration rate

Table 6-8. Median C/T AUC_{0-8} in Virtual Pediatric cUTI and cIAI Patients 2 to <18 Years Relative to Pediatric Virtual Population with eGFR >50 mL/min/1.73m^2 by Renal Function Category (Fold Difference)

Infection	Drug	eGFR (mL/min/1.73m^2	2 to <6y	6 to <12y	12 to <18y
cUTI	Ceftolozane	30 to 50	1.34	1.31	1.33
		15 to <30	1.02	1.03	1.02
		Receiving IHD	1.94	1.97	2.39
	Tazobactam	30 to 50	1.20	1.13	1.18
		15 to <30	0.86	0.87	0.85
		Receiving IHD	0.91	0.90	1.05
cIAI	Ceftolozane	30 to 50	1.35	1.31	1.32
		15 to <30	1.02	1.03	1.02
		Receiving IHD	1.98	2.00	2.45
	Tazobactam	30 to 50	1.20	1.13	1.18
		15 to <30	0.86	0.87	0.85
		Receiving IHD	0.91	0.90	1.05

Source: Adapted from Report 08wwfz.pdf-Tables 44-51
Abbreviations: cUTI- complicated urinary tract infections, cIAI- complicated intra-abdominal infection, y- year, IHD- intermittent hemodialysis, eGFR- estimated glomerular filtration rate

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The clinical safety data were derived from one open label, non-comparative, multi-center clinical study that evaluated the safety, tolerability and PK of C/T in hospitalized pediatric participants from birth (>32 weeks GA and ≥7 days postnatal) to <18 years of age with HABP/VABP (P036). The clinical efficacy data and safety data were extrapolated from the adult HABP/VABP clinical trial (PN008) as the course of the disease, and the effects of the drug are sufficiently similar in adult and pediatric patients. Table 7-1 provides additional information on these clinical trials.

Table 7-1. Listing of Clinical Trials Relevant to this sNDA

Study Number (Clinicaltrials.gov Identifier)	Type of Study	Group/Dose/No. of Participants Enrolled			Study Endpoints	Design	Study Population
Studies to Support Safety							
Study P036 (NCT04223752)	Phase 1, open-label, non-comparative, multi-center study for treatment of **HABP/VABP**	Group 1 (12 to <18 years	TOL 2 g and TAZ 1 g	8 participants	Primary: • AEs • AEs leading to discontinuation of study intervention Secondary: • Plasma concentrations of each time point for TOL and TAZ • Steady-state plasma area under the concentration time curve of an 8-hour dosing interval, C_{max}, $t_{1/2}$, Vd and CL for TOL and TAZ	Treatment duration: 8-14 days Follow-up period: 14 days after last dose of study intervention 12 site (8 countries)	Male and female hospitalized pediatric participants (birth to <18 years of age) with HABP/VABP Sex (overall): Male 52.5% Female 47.5% Age – overall median age (range): 2.96 years (0.03 to 16.64 years)
		Group 2 (7 to <12 years)	TOL 40 mg/kg and TAZ 20 mg/kg	7 participants			
		Group 3 (2 to <7 years)	TOL 40 mg/kg and TAZ 20 mg/kg	8 participants			
		Group 4 (3 months to <2 years)	TOL 40 mg/kg and TAZ 20 mg/kg	10 participants			
		Group 5* (Birth to <3 months)	TOL 40 mg/kg and TAZ 20 mg/kg	7 participants			
Studies to Support Efficacy and Safety							
Study PN008 (NCT02070757)	Phase 3, prospective,	Ceftolozane/tazobactam 3 g (TOL 2g and TAZ 1 g) q8h IV or Meropenem 1 g q8h IV			Primary: • Day 28 all-cause	Treatment duration: 8-14	Male/female Age:

	randomized, double blind multicenter study	Ceftolozane/tazobactam 3 g: 361 patients Meropenem 1 g: 359 patients	mortality in the intent-to-treat population Secondary: • Clinical response at the test of cure visit in the intent-to-treat population	days Follow up period: 28-35 days after end-of-treatment visit 119 sites (29 countries)	≥18 years Subjects with VABP and ventilated HABP stratified by diagnosis and by age (≥65 or <65 years)

* Birth included newborns at 33 weeks post-menstrual age (>32 weeks GA and ≥ 7 days postnatal)
Abbreviations: HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; AE, adverse event; TOL, ceftolozane; TAZ, tazobactam; MTZ, metronidazole; MERO, meropenem
Source: Reviewer generated based on 2.7.4 Summary of Clinical Safety, Clinical Study Report MK-7625A-036 and S-008 Review

7.2. Review Strategy

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

The efficacy of ZERBAXA for treatment of HABP/VABP in pediatric patients was extrapolated from the adult clinical study (PN008) and supported by pediatric PK data obtained from the current study. Study P036 was designed with the primary objective to evaluate the safety, tolerability and PK of ZERBAXA in pediatric participants from birth (>32 weeks GA and ≥ 7 days postnatal) to less than 18 years of age with HABP/VABP. Forty participants received at least one dose of C/T. Safety results are presented using descriptive statistics. Data sources reviewed included the patient-level datasets, study reports, protocols, and case report forms. The SDTM and ADaM datasets are available at the following location in the Agency's Electronic Document Room:
\\CDSESUB1\evsprod\NDA206829\0910\m5\datasets\p036mk7625a\analysis\adam\datasets

The quality of submitted data was sufficient for review purposes. It was possible to reproduce the Applicant's main analysis results without complex manipulations.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Adult HABP/VABP Study PN008

Trial Design

The efficacy of ZERBAXA in pediatric patients with HABP/VABP was extrapolated from the adult HABP/VABP study (PN008), as the pathophysiology of HABP/VABP and the responsible pathogens are similar in both populations. Following is a summary of study PN008.

Study PN008 was a randomized, double-blind, multicenter, active-controlled non-inferiority study designed to assess the efficacy and safety of C/T compared to meropenem in the treatment of adult subjects with HABP/VABP.

The study's main goal was to establish that C/T was not inferior to meropenem in treating adult patients with HABP/VABP. This was assessed by comparing 28-day all-cause mortality rates between treatment groups in the intent-to-treat population, applying a non-inferiority margin of 10%. An important secondary objective was to evaluate clinical response rates between C/T and meropenem among adult HABP/VABP patients in the intent-to-treat population during the test-of-cure assessment, conducted 7 to 14 days following completion of treatment.

Study Endpoints

The main efficacy measure was all-cause mortality on Day 28 within the intent-to-treat population. The additional efficacy measure examined clinical outcomes during the test-of-cure visit among intent-to-treat participants. Clinical outcomes were determined by evaluating the presence of clinical indicators and manifestations of hospital-acquired or ventilator-associated bacterial pneumonia, whether supplementary antimicrobial treatment was required for HABP/VABP beyond permitted adjunctive therapies, and patient survival. A positive clinical outcome was defined as achieving clinical cure.

Efficacy Results

The Day 28 all-cause mortality rates were 24.0% for C/T and 25.3% for meropenem. The mortality rate for meropenem is similar to the active control rates used to justify the non-inferiority margin included in the HABP/VABP guidance. The stratified difference (meropenem - C/T) in the mortality rates was 1.1% with a corresponding stratified 95% confidence interval for the difference of (-5.1%, 7.4%). Since the lower limit of the confidence interval is greater than the non-inferiority margin of -10%, C/T met the prespecified criteria for demonstrating non-inferiority to meropenem. Refer to unireview of supplemental NDA 8 (dated May 31, 2019) for further details.

Refer to section 6.2 for further information regarding evidence of effectiveness.

8.1.2. Pediatric HABP/VABP Study P036

Trial Design

The phase 1 study was an open-label, non-comparative, multicenter clinical study to evaluate the safety, tolerability and pharmacokinetics of C/T in pediatric participants, from birth (>32 weeks GA and ≥7 days postnatal) to <18 years old, with HABP/VABP. The trial did not assess efficacy and therefore this section will discuss the trial design and the results pertaining to the safety population. The pediatric efficacy was extrapolated from the adult HABP/VABP clinical trial described in section 8.1.1.

The study was conducted at 12 centers across eight countries. The total study duration for each participant was approximately 30 days, from the documentation of informed consent through the final follow-up. Participants received C/T, administered as a 1-hour intravenous (IV) infusion every eight hours, as an add-on to standard-of-care therapy. The duration of C/T administration was 8 to 14 days. Following the treatment period, each participant entered a 14-day follow-up period.

Participants were stratified by age group prior to receiving treatment with the study drug. There were five pediatric age groups evaluated in the study:

- Group 1: Adolescents (12 to <18 years old)
- Group 2: Older children (7 to <12 years old)
- Group 3: Younger children (2 to <7 years old)
- Group 4: Infants and toddlers (3 months to <2 years old)
- Group 5: Neonates and young infants (birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months old)

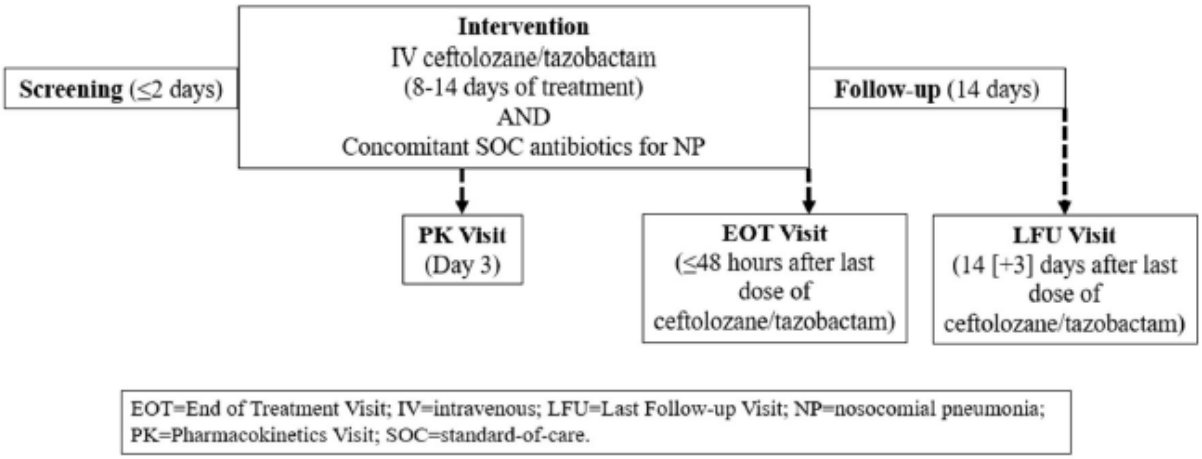
After the first 3 participants were enrolled into a given age group, enrollment was paused for that age group to allow for an interim PK analysis to confirm or modify the proposed pediatric dose for the remaining participant in that age group. The interim analyses of PK data confirmed the initial dosing recommendations for all age groups: Groups 1-5, with no modifications introduced. See **Figure 8-1** for a depiction of the study design.

A total of 41 participants were enrolled in the study, with 40 participants included in the safety analysis population in the following age groups:

- Group 1: 8 pediatric patients enrolled
- Group 2: 7 pediatric patients enrolled
- Group 3: 8 pediatric patients enrolled
- Group 4: 10 pediatric patients enrolled

- Group 5: 7 pediatric patients enrolled

Figure 8-1. Study Design for Study P036



Source: Applicant Final Protocol for Study MK-7625A-036-00

Key Inclusion Criteria

1. Has diagnosis of proven or suspected nosocomial pneumonia (NP) (including HABP/VABP), as determined by the investigator
2. Is hospitalized and anticipated to receive a minimum of 8 days of concomitant standard of care (SOC) antibiotic therapy for proven or suspected NP
3. Is male or female from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age inclusive, at the time of signing the informed consent/assent

Key Exclusion Criteria

1. Has a documented history of any moderate or severe hypersensitivity reaction to any β-lactam antibacterial
2. Has moderate to severe impairment of renal function
3. Is receiving or anticipated to receive piperacillin-tazobactam while receiving C/T or has received piperacillin-tazobactam within 24 hours prior to the first dose of C/T
4. Has one or more of the following laboratory abnormality
    a. Absolute neutrophil count <1000 mm^3
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 x the upper limit of normal (ULN)
    c. Total bilirubin ≥2 x ULN
5. Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the participant

6. Has any rapidly progressing disease or immediately life-threatening illness including active hepatic failure or septic shock
7. Has active immunosuppression

Table 8-1 shows the schedule of events for the trial.

Table 8-1. Schedule of Safety Assessments

Study Period	Screening	Intervention					Follow-up	Notes
Visit Number/Title	1 Screening	2 Allocation	3	4 PK Visit	5-15	16 EOT Visit	17 LFU Visit	Visits 1 and 2 can be on the same day. Visit 17 can be by telephone; in-person visit required for AE or abnormal laboratory follow up.
Scheduled Day:	≤48 hours prior to first dose of ceftolozane/ tazobactam	Day 1	Day 2	Day 3	Day 4-14	≤48 hours after last dose of ceftolozane/ tazobactam	14 days after last dose of ceftolozane/ tazobactam	
Scheduled Window:	--	--	--	+2 days	--	--	+3 days	
Safety Procedures								
Full physical examination	X							
Height	X							
Weight	X							
Directed Physical Examination		X	X	X	X	X		Can also be performed whenever medically necessary.
Vital Signs	X	X	X	X	X	X		Heart rate, blood pressure, respiratory rate, and temperature. If Visit 1 and 2 occur on the same day, does not need to be performed twice.
Urine or Serum Pregnancy Test (WOCBP only)	X							Collect per local guidance.
Blood for Hematology and Chemistry Safety Evaluations	X	X	X	X	X	X	X	Required for Visits 1, 4, and 16. Only collect if clinically indicated at Visits 2, 3, 5-15, and 17.
Assessment of CrCL	X	X	X	X	X	X	X	Required for Visit 1 and only if clinically indicated at all other visits. See Section 8.3.4.1 – Assessment of Creatinine Clearance
AE/SAE Monitoring		X	X	X	X	X	X	
Pharmacokinetics								
Plasma PK sampling				X				Number of samples and timing is described in Section 8.6.1.
AE=adverse event; CrCL=creatinine clearance; EOT=end of treatment; IV=intravenous; LFU=last follow-up; NP=nosocomial pneumonia; PK=pharmacokinetics; q8h=every 8 hours; SAE=serious adverse event; SOC=standard-of-care; WOCBP=woman/women of childbearing potential.								

Source: Applicant Final Protocol for Study MK-7625A-036-00

Study Endpoints

The primary study endpoint was to evaluate safety by monitoring adverse events (AEs). These adverse events included any adverse event reported including any serious AEs, any drug-related AEs, any serious drug-related AEs, and any AE that led to discontinuation of study intervention.

The secondary endpoints included:

- Plasma concentrations at each time point for ceftolozane and tazobactam
- Steady state plasma area under the concentration-time curve of an 8-hour dosing interval (AUC_{0-8}), maximum observed concentration during a dosage interval (C_{max}), elimination half-life ($t_{1/2}$), volume of distribution (V_d), and clearance (CL) for ceftolozane and tazobactam

Statistical Analysis Plan

The safety and tolerability were assessed using the safety population which consisted of all participants who received any dose of C/T. Six participants in each cohort was considered an adequate sample size for assessment of safety and PK sampling. All analyses were descriptive and no formal hypothesis testing was performed.

Protocol Amendments

Two amendments were made to the protocol.

The first amendment, received on May 5, 2020, revised the guidance on contraceptive use. This change removed the "acceptable contraceptive methods" option to align the protocol with recommendations from the Clinical Trial Facilitation Group (CTFG) for trials involving investigational products with a potential risk of human teratogenicity or fetotoxicity in early pregnancy. Additionally, this amendment updated the definition of an overdose to ensure consistency across the C/T program.

The second amendment, received on December 12, 2022, changed the end-of-study definition from Last Participant, Last Visit (LPLV) to Last Data Available (LDA). This revision was implemented to facilitate the data collection and evaluation necessary to fulfill regulatory requirements.

8.1.3. Study Results of Study P036

Compliance with Good Clinical Practices

The Applicant states in Study P036's clinical study report: "This study was conducted in accordance with local and/or national regulations (including all applicable data protection laws and regulations), ICH GCP, and the ethical principles that have their origin in the Declaration of Helsinki regarding IEC review, informed consent and the protection of human participants in biomedical research."

Financial Disclosure

The Applicant submitted the required Financial Disclosure information. There were no significant financial conflicts of interest identified among the study site investigators. See Section 15.1for further information.

Patient Disposition

Patient disposition is described in **Table 8-2**. Of the 40 enrolled participants, 38 participants (95%) completed the study treatment with C/T and 2 participants (5.0%) were discontinued early based on the clinical improvement at the discretion of the treating physician. There were 3 participants (7.5%) who died after completing the study treatment. Refer to Section 8.2.4 for further information.

Table 8-2. Patient Disposition (Safety Population)

	Group 1 12 - <18 y N=8 n (%)	Group 2 7 - <12 y N=7 n (%)	Group 3 2 - <7 y N=8 n (%)	Group 4 3 mo - <2 y N=10 n (%)	Group 5 Birth - <3 mo N=7 n (%)	Total N=40 n (%)
Completed treatment	8 (100)	7 (100)	7 (87.5)	10 (100)	6 (85.7)	38 (95)
Discontinued	0	0	1 (12.5)	2 (20)	2 (28.6)	5 (12.5)
Death	0	0	0	2 (20)	1 (14.3)	3 (7.5)
Withdrawal by physician	0	0	1 (12.5)	0	1 (14.3)	2 (5.0)

Source: Adapted from CSR Table 10-1
Abbreviations: y, years; mo, months

Protocol Violations/Deviations

Table 8-3 identifies the important protocol violations that occurred during the study. In total, there were 9 participants (22.5%) that had important protocol deviations. The protocol deviation that was reported most frequently (12.5%) was related to trial procedures where participants missed collection of one or more required safety laboratory assessments at Screening, Day 3 and end-of-treatment (EOT) visit.

Table 8-3. Important Protocol Deviations

	Group 1 12 - <18 y N=8 n (%)	Group 2 7 - <12 y N=7 n (%)	Group 3 2 - <7 y N=8 n (%)	Group 4 3 mo - <2y N=10 n (%)	Group 5 Birth - <3 mo N=7 n (%)	Total N=40 n (%)
One or more important protocol deviation	**0**	**0**	**3 (37.5%)**	**3 (30%)**	**3 (42.9%)**	**9 (22.5%)**
Discontinuation Criteria	**0**	**0**	**0**	**1 (10%)**	**0**	**1 (2.5%)**
Participant developed	0	0	0	1 (10%)	0	1 (2.5%)

study intervention discontinuation criteria, but was not discontinued from study intervention						
Inclusion/Exclusion Criteria	**0**	**0**	**0**	**0**	**2 (28.6%)**	**2 (5.0%)**
Participant did not meet all eligibility criteria	0	0	0	0	2 (28.6%)	2 (5.0%)
Trial Procedures	**0**	**0**	**2 (25%)**	**2 (20%)**	**1 (14.3%)**	**5 (12.5%)**
Missed collection of 1 or more critical safety laboratory assessments at Screening, Day 3 and/or EOT visit	0	0	1 (12.5%)	2 (20%)	0	3 (7.5%)
LFU visit was missed or held outside of the allowable window defined in the protocol	0	0	1 (12.5%)	0	1 (14.3%)	2 (5.0%)
Safety Report	**0**	**0**	**1 (12.5%)**	**0**	**0**	**1 (12.5%)**
Reportable safety event and/or follow up Safety Event information was not reported per the timelines outlined in the protocol	0	0	1 (12.5%)	0	0	1 (12.5%)

Source: Adapted from CSR Table 14.1-3 and Table 16.2.2
Note: Every participant is counted a single time for each applicable row and column.
Abbreviations: y, years; mo, months; EOT, end-of-treatment

Table of Demographic Characteristics

Table 8-4 shows the demographic and baseline characteristics for participants included in the safety population of Study P036. Overall, the majority of participants were white and from the Ukraine. Approximately half the participants were female.

Table 8-4. Demographic and Baseline Characteristics (Safety population, APaT)

Demographic Parameters	**Total** N=40 n (%)
Sex	
Male	21 (52.5)
Female	19 (47.5)
Age	

Mean years (SD)	5.4 (5.7)
Median (years)	3.0
Min, max (years)	0.03, 16.6
Age Group	
Group 1 (12 to <18 years)	8 (20)
Group 2 (7 to <12 years)	7 (17.5)
Group 3 (2 to <7 years)	8 (20)
Group 4 (3 months to <2 years)	10 (25)
Group 5 (birth to <3 months)	7 (17.5)
Race	
White	30 (75)
Multiple	5 (12.5)
American Indian or Alaska Native	3 (7.5)
Black or African American	2 (5)
Ethnicity	
Hispanic or Latino	14 (35)
Not Hispanic or Latino	26 (65)
Country	
Chile	2 (5)
Colombia	7 (17.5)
Estonia	2 (5)
Greece	1 (2.5)
Mexico	1 (2.5)
South Africa	1 (2.5)
Spain	6 (15)
Ukraine	20 (50)

Source: Reviewer table, partially adapted from CSR Table 10-3
Abbreviations: N, total number of participants; n, total number of participants meeting criteria; SD, standard deviation

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 8-5 presents baseline characteristics such as height, weight, and baseline creatinine. Group 1 (participants aged 12 years and older) tended to have the highest values for height, weight, and baseline creatinine compared to the other age groups. However, Group 5, which comprised neonates and infants younger than 3 months, had a wider range of baseline creatinine. This variability is partly explained by the influence of maternal creatinine, which crosses the placenta. Additionally, neonates have immature renal function, characterized by low glomerular filtration rates (GFR) and immature tubular structures, which contributes to the backflow of creatinine.[10]

Table 8-5. Baseline Characteristics (Safety Population)

Baseline Parameters	Group 1 12 - <18 y N=8 n (%)	Group 2 7 - <12 y N=7 n (%)	Group 3 2 - <7 y N=8 n (%)	Group 4 3 mo - <2 y N=10 n (%)	Group 5 Birth - <3 mo N=7 n (%)	Total N=40 n (%)
Height (cm)						
Mean (SD)	165.8 (10.8)	133.3 (27.7)	97.8 (8.9)	68.3 (10.3)	50.9 (6.7)	102 (44.3)
Median (range)	167.5 (147 – 184)	124 (97 – 170)	98 (79 – 110)	68 (53 – 82)	54 (39 – 56)	97 (39 – 184)
Weight (kg)						
Mean (SD)	58 (17.9)	36.1 (22.1)	13.7 (3.3)	7.1 (3)	3.6 (1)	23 (23.9)
Median (range)	58 (35 – 90)	28 (13.6 – 73)	14.5 (7.9 – 17)	7 (3.3 – 12)	3.8 (2.1 – 4.8)	13.3 (2.1 – 90)
Baseline Cr (mg/dL)						
Mean (SD)	0.43 (0.14)	0.43 (0.14)	0.27 (0.12)	0.30 (0.15)	0.42 (0.40)	0.36 (0.22)
Median (range)	0.39 (0.29 – 0.78)	0.40 (0.29 – 0.73)	0.30 (0.1 – 0.42)	0.23 (0.14 – 0.67)	0.26 (0.16 – 1.3)	0.30 (0.1 – 1.3)
Prior antibacterial drug use						
Yes	8 (100%)	7 (100%)	8 (100%)	10 (100%)	7 (100%)	40 (100%)

Source: Partially adapted from CSR Table 10-3 and OCS Analysis Studio v2.1.6, Custom Table
Abbreviations: y, years; mo, months; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

A total of 40 participants were enrolled and received C/T. There were 2 participants (5%) who had early discontinuation of therapy after 5 days at the discretion of the investigators, due to

[10] Guignard JP, Drukker A. Why do newborn infants have a high plasma creatinine? Pediatrics. 1999 Apr;103(4):e49. doi: 10.1542/peds.103.4.e49.

improvement in symptoms. Refer to Applicant's response to the information request submitted on January 28, 2026. In total 38 participants (95%) received the C/T every eight hours for approximately 8 to 14 days.

Table 8-6 presents the use of concomitant medications in the safety population. All patients received the study drug, C/T, in addition to standard-of-care therapy. The four most frequently reported concomitant antibacterial drugs were meropenem (35%), meropenem trihydrate (30%), vancomycin (30%), and colistimethate sodium (17.5%).

Table 8-6. Concomitant Antibacterial Use, Safety Population

Concomitant Antibacterials for systemic use	**Group 1 12 - <18 y N=8 n (%)**	**Group 2 7 - <12 y N=7 n (%)**	**Group 3 2 - <7 y N=8 n (%)**	**Group 4 3 mo - <2 y N=10 n (%)**	**Group 5 Birth - <3 mo N=7 n (%)**	**Total N=40 n (%)**
Amikacin	0	1 (14.3%)	0	0	0	1 (2.5%)
Amoxicillin trihydrate; clavulanate potassium	0	0	1 (12.5%)	0	0	1 (2.5%)
Amoxicillin; clavulanate acid	0	0	1 (12.5%)	0	0	1 (2.5%)
Avibactam sodium; ceftazidime pentahydrate	0	0	0	1 (10%)	1 (14.3%)	2 (5%)
Avibactam; ceftazidime	0	0	0	2 (20%)	0	2 (5%)
Cefazoline	0	0	1 (12.5%)	0	1 (14.3%)	2 (5%)
Cefepime	0	2 (28.6%)	0	0	1 (14.3%)	3 (7.5%)
Cefotaxime	0	0	0	0	1 (14.3%)	1 (2.5%)
Ceftazidime	0	1 (14.3%)	0	0	0	1 (2.5%)
Ceftriaxone	2 (25%)	0	0	0	0	2 (12.5%)
Ciprofloxacin	1 (12.5%)	0	0	3 (30%)	1 (14.3%)	5 (12.5%)
Colistimethate sodium	0	0	1 (12.5%)	5 (50%)	1 (14.3%)	7 (17.5%)
Colistin	0	0	1 (12.5%)	0	0	1 (2.5%)
Gentamicin	0	1 (14.3%)	0	0	0	1 (2.5%)
Gentamicin	0	0	0	1 (10%)	0	1 (2.5%)

sulfate						
Levofloxacin	0	0	0	1 (10%)	0	1 (2.5%)
Linezolid	0	0	0	2 (20%)	1 (14.3%)	3 (7.5%)
Meropenem	1 (12.5%)	4 (57.1%)	1 (12.5%)	5 (50%)	3 (42.9%)	14 (35%)
Meropenem trihydrate	5 (40%)	2 (28.6%)	2 (25%)	3 (30%)	1 (14.3%)	12 (30%)
Metronidazole	1 (12.5%)	0	0	1 (10%)	0	2 (5%)
Moxifloxacin hydrochloride	0	0	0	1 (10%)	0	1 (2.5%)
Piperacillin; tazobactam	1 (12.5%)	0	0	0	0	1 (2.5%)
Sulfamethoxazole; trimethoprim	1 (12.5%)	0	1 (12.5%)	2 (20%)	0	4 (10%)
Teicoplanin	0	0	0	1 (10%)	0	1 (2.5%)
Tobramycin	1 (12.5%)	0	0	0	1 (14.3%)	2 (5%)
Vancomycin	1 (12.5%)	4 (57.1%)	1 (12.5%)	4 (40%)	2 (28.6%)	12 (30%)

Sources: Partially adapted from CSR Table 14.1-10
Abbreviations: y, year; mo, month

Efficacy Results – Primary Endpoint

The purpose of this study was to evaluate the safety, tolerability and PK for C/T in pediatric patients under the age of 18 years with HABP/VABP. This study was not designed to support efficacy. All data on treatment efficacy is extrapolated from the adult HABP/VABP clinical trial (PN008), which is discussed in Section 8.1.1.

Data Quality and Integrity

The quality of submitted data was sufficient for review purposes. It was possible to reproduce the Applicant's main safety analysis without complex manipulations.

8.1.4. Integrated Assessment of Effectiveness

The efficacy of ZERBAXA for treating HABP/VABP in pediatric patients is extrapolated from the efficacy data in adult patients. The mechanism of action of ZERBAXA and the disease pathophysiology and clinical manifestations are sufficiently similar to support extrapolation of effectiveness from adults to pediatric populations for the indication of HABP/VABP. The pediatric clinical study P036 focused on safety, tolerability, and pharmacokinetic data in pediatric participants with HABP/VABP and was not designed and powered to support efficacy. However, the PK data from Study P036 for pediatric patients aged from birth (at least 33 weeks post-menstrual age) to 18 years of age and PopPK modeling to determine the optimal dosing regimen to achieve ZERBAXA exposures associated with efficacy in adult trials were used to

extrapolate the efficacy of ZERBAXA for treating HABP/VABP in pediatric patients from the efficacy demonstrated in adults.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of ZERBAXA in pediatric patients with HABP/VABP is based on Study P036 (MK-7625A-036) that evaluated the safety, tolerability, and pharmacokinetics of ZERBAXA in pediatric patients with HABP/VABP. Supporting safety evidence originates from the established safety profile of ZERBAXA in adult patients with HABP/VABP, which was reviewed in sNDA 008. Additional supporting safety data are available from pediatric patients with cIAI and cUTI, which were reviewed in sNDA 011 and sNDA 012, respectively. Please refer to the reviews of these sNDAs for further information on the safety of ZERBAXA in these populations.

The current safety review focuses on findings from Study P036, a phase 1, open-label, non-comparative, multicenter study that evaluated the safety, tolerability, and pharmacokinetics of ZERBAXA in pediatric patients from birth (>32 weeks GA and ≥7 days postnatal) to less than 18 years of age with HABP/VABP. Safety assessments were conducted from the start of treatment through the follow-up visit, which occurred 14 (±3) days after the last dose of the study drug. The safety data from the 40 pediatric participants who received at least one dose of ZERBAXA are reviewed below.

A summary of the adverse events from the trial (P036) is presented below.

Table 8-7. Summary of Adverse Events in the Treated Population, P036

	Ceftolozane/tazobactam N=40
Event Category	**n (%)**
SAE	8 (20.0)
Deaths	3 (7.5)
Discontinuation due to AE	0
Any discontinuations	2 (5.0)
AE related to study drug	1 (2.5)
Any AE	30 (75.0)
Severe	5 (12.5)
Moderate	10 (25.0)
Mild	15 (37.5)

Source: adae.xpt; Software: MS Excel
Treatment emergent adverse events defined as an AE that has a start date on or after the first dose of study drug, or it has a start date before the date of the first dose of study drug but worsens in severity on or after the first dose date of study drug through 14 days following cessation of study drug treatment.

Duration of treatment is between 8 to 14 days. Study duration is from the first dose of study drug to approximately 14 days following cessation of study drug including follow-up.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

8.2.2. Review of the Safety Database

Overall Exposure

In total, 40 pediatric participants were exposed to C/T in the P036 (HABP/VABP) study. All participants received C/T, as well as standard of care therapy. As stated previously, the median age of pediatric participants exposed to C/T was 2.9 years old and the range was 10 days old to 16.6 years old. The mean age of C/T exposed patients was 5 years (63 months). There was only one infant enrolled in the study who was preterm with a gestational age of 34 weeks 0 days and a post-menstrual age of 35 weeks and 4 days at the time of enrollment. The numbers of participants by age group in Study P036 are listed in Table 8-8.

Table 8-8. Exposure to ZERBAXA by Age Group, Safety Population

	Number of participants exposed to C/T	Dose of C/T received
Group 1: 12 to <18 years	8	Ceftolozane 2 g and tazobactam 1 g
Group 2: 7 to <12 years	7	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg
Group 3: 2 to <7 years	8	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg
Group 4: 3 month to <2 years	10	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg
Group 5: birth (>32 weeks gestational age and ≥7 days postnatal) to <3 months	7	Ceftolozane 40 mg/kg and tazobactam 20 mg/kg

Source: Reviewer table

Adequacy of the Safety Database

While the safety database was small, it was considered acceptable in terms of the number of subjects in each predefined age group, given the known safety profile of C/T and difficulties in recruiting hospitalized pediatric patients that meet the clinical definition for HABP/VABP. Safety evaluations included vital signs, routine physical examinations, and laboratory tests. Participants were monitored for adverse events. Adverse events of special interest (elevated liver enzymes meeting specific criteria (DILI) and events of ZERBAXA overdose) were identified

and recorded.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Case report forms were reviewed to assess the consistency of the data submitted. The reported terms for Adverse Events (AEs) matched the MedDRA dictionary terms version 27.0 used during the study.

Categorization of Adverse Events

The severity of the AEs were characterized as:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated)
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
- Severe: An event that prevents normal everyday activities. An AE that is assessed is severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other important medical events

The time period for collection of AEs for each participant ranged from the time the participant enrolled in the study through a minimum of 14 days after the last administration of the investigational drug. All serious and nonserious AEs were recorded in the case report form (CRF) and SAEs were reported to the Applicant within 24 hours of onset. Causality assessments were performed by the investigator for all AEs (serious and non-serious).

MO Comment*: The categorization of the severity of adverse events was adequate.*

Routine Clinical Tests

Routine chemistry (Blood urea nitrogen (BUN), creatinine, sodium, potassium, bicarbonate, chloride, glucose, calcium, phosphorus, aspartate aminotransferase (AST), alanine

aminotransferase (ALT), total bilirubin (and direct bilirubin if total bilirubin is elevated above the upper limit of normal), albumin, total protein, alkaline phosphatase) and hematology (platelet count, hemoglobin, hematocrit, leukocytes with differential [neutrophils, band neutrophils, lymphocytes, monocytes, eosinophils, basophils]) laboratory tests were obtained.

MO Comment: *The routine clinical tests were adequate.*

8.2.4. Safety Results

Deaths

There were three deaths reported after the end of treatment, during the follow-up period. The three deaths occurred 4, 8, and 11 days after completion of study drug, respectively. All deaths were assessed as unrelated to study intervention by the investigator and attributed to severe underlying conditions.

MO Comment*: As reviewed in detail in the following narratives, I agree with the study investigators that these deaths were not related to C/T and all three deaths can be attributed to the participants' severe underlying medical comorbidities.*

The following case narratives describe the events in greater detail.

- Participant (b) (6) (SAE: Septic shock)
  A 9-month-old male with a severe underlying diagnosis of spinal muscular atrophy (SMA) type 1 was hospitalized for multiple comorbidities, including a swallowing disorder, spinal cord degeneration, arterial hypertension, and epilepsy. Eight days prior to study enrollment, he was already being treated for NP with vancomycin and meropenem. He was then enrolled in the clinical study and started on C/T. This was administered concomitantly with a complex antibacterial regimen that included vancomycin, meropenem, and sulfamethoxazole-trimethoprim, in addition to antihypertensives. During the nine-day course of study treatment, the patient experienced moderate hypoxia on Day 4 and developed anemia (hemoglobin 6.99 g/dL) on Day 6, which required a red blood cell transfusion. He completed the full course of C/T on Day 9.

  In the days following the completion of study treatment, the patient developed new complications, including a skin infection and phlebitis on Day 13. A significant deterioration occurred with the identification of new, severe infections: 1) on Day 17, a blood culture was positive for *Candida auris*, 2) concurrently, a urine culture grew *Serratia marcescens*. He was diagnosed with systemic mycosis on Day 19 and started on caspofungin. The patient's condition rapidly declined on Day 21. He was diagnosed with

urinary tract infection (UTI) with sepsis, and his laboratory results showed a sharp increase in his white blood cell count (to 26.7 × 10^9/L) and evidence of acute liver injury (ALT 4.1 µkat/L, >6x ULN). Treatment with ceftazidime-avibactam was initiated. Later that day, he suffered a cardiorespiratory arrest preceded by bradycardia, desaturation, and hypotension. Despite a 20-minute advanced resuscitation effort, he could not be revived. The subject died due to cardiorespiratory arrest secondary to septic shock, which was attributed to both pulmonary and urinary sources.

***MO comment**: I concur with the investigators' assessment that the events of death and septic shock are unlikely to be related to C/T, as they occurred 11 days after the study intervention was discontinued. Broad-spectrum antimicrobials can increase the risk of fungal infections by disrupting the normal microbial flora and reducing bacterial competition. Since this participant received multiple broad-spectrum antimicrobials—including C/T, meropenem, linezolid, gentamicin, colistimethate, and moxifloxacin—it is plausible that the combination of these agents contributed to the increased risk of developing an invasive fungal infection.*

- Participant (b) (6) (SAE: Cardiogenic shock)
  A 51-day-old male twin, born at 37 weeks, had a complex medical history including a dysmorphic syndrome, severe bronchopulmonary dysplasia, and complex congenital heart disease (double outlet right ventricle with pulmonary atresia). During his hospitalization, he was diagnosed with NP and began treatment with C/T and concomitant cefepime. His baseline labs were notable for a mildly elevated total bilirubin (18.8 µmol/L). During the study treatment, the patient developed a catheter-associated bloodstream infection on Day 10 and was started on vancomycin. He completed the C/T course on Day 12. The following day (Day 13), his condition worsened with the diagnosis of an inferior vena cava thrombosis and cardiac dysfunction. His bilirubin levels had increased (total: 30.61 µmol/L (>1.5xULN); direct: 20.19 µmol/L), though his liver enzymes remained normal. On Day 15, the patient experienced a sudden hemodynamic deterioration with tachycardia (160 bpm), tachypnea, and hypotension (63/22 mmHg), leading to a diagnosis of cardiogenic shock. He was started on an epinephrine infusion. An echocardiogram confirmed mild myocardial dysfunction and the vena cava thrombus. A decision was made for surgical intervention, but prior to the procedure, he suffered a cardiac arrest. Advanced resuscitation successfully restored circulation after five minutes. The patient underwent a surgical procedure to create a systemic-pulmonary artery fistula under general anesthesia with cardiopulmonary bypass. The surgery was complicated by several severe events:

- While attempting to wean from bypass, he developed hypoperfusion, refractory metabolic acidosis, and ventricular fibrillation, requiring defibrillation.
- He required significant vasopressor support (epinephrine and norepinephrine) to maintain his blood pressure.
- Due to blood loss (50 mL) and anemia (hgb 11.6 g/dL), he received transfusions of red blood cells and platelets.

Following surgery, he was transferred to the NICU. The next day, his hemodynamic instability continued, and he suffered a second episode of ventricular fibrillation, requiring two more defibrillations. He then developed profound bradycardia (heart rate 40 bpm), which progressed to another cardiac arrest. Despite an 8-minute advanced resuscitation effort, he experienced a final cardiac arrest and developed asystole. After a further 10 minutes of resuscitation without return of spontaneous circulation, care was withdrawn. The subject died due to severe cardiogenic shock.

MO Comment: *I concur with the investigators' assessment that the events of death and cardiogenic shock are unlikely to be related to C/T. These events are more plausibly attributed to the participant's underlying congenital heart disease and congenital pulmonary atresia. Repeat bilirubin and liver enzyme levels were not measured after the end of treatment. However, the elevated bilirubin is likely attributable to complications related to the vena cava thrombus, rather than to treatment with C/T.*

- Participant (b) (6) (SAE: Myocardial depression, omentitis, intestinal obstruction, febrile convulsions, multiple organ dysfunction syndrome)
  An 11-month-old male was hospitalized for a perforated Meckel's diverticulum. One week after admission, he was diagnosed with NP, enrolled in the clinical study, and began treatment with C/T, administered concomitantly with meropenem. The patient's condition acutely deteriorated on Day 9 of treatment. He developed a high fever (39.8 °C), restlessness, and intestinal paresis with abdominal bloating. An abdominal ultrasound revealed omental edema and infiltration, leading to a diagnosis of omentitis. This was complicated by multiple infections: 1) a culture from the abdominal wall tissue grew *Enterobacter aerogenes*; 2) blood cultures were positive for *Acinetobacter baumannii*, which was attributed to his subclavian catheter. Empiric treatment with linezolid was added. On Day 10, he underwent a laparotomy for lysis of adhesions and an omentectomy, where surgeons noted a swollen, purulent omentum. Despite these interventions, the patient's condition continued to worsen. On Day 12, he experienced a one-hour-long febrile convulsion (max temperature 40 °C), which was treated with diazepam and paracetamol. Gentamicin was added to his antimicrobial regimen. By Day 14, he had developed abdominal compartment syndrome, a non-functioning stoma, and

decreased urine output. Laboratory work revealed severe thrombocytopenia (platelet count 57 × 10^9/L). He was diagnosed with a severe intestinal obstruction, and his antibacterial therapy was changed to moxifloxacin, metronidazole, and colistimethate sodium. He returned to the operating room for a second laparotomy, which involved intestinal intubation, creation of a controlled laparostomy, and abdominal drainage. Following this procedure, he suffered an episode of severe myocardial depression with profound bradycardia (HR 44 bpm) and hypotension (63/42 mmHg). He required aggressive resuscitation with vasopressors, inotropes, and other supportive medications, including blood products. The cardiovascular event resolved after 10 minutes. The patient completed the 15-day course of C/T. However, his clinical decline progressed. On Day 17, he was diagnosed with severe multiple organ dysfunction syndrome (MODS), characterized by: 1) dependence on mechanical ventilation, 2) oliguria, 3) worsening intestinal paresis; 4) pancytopenia, with his white blood cell count falling to 3.4 × 10^9/L and platelets to 2 × 10^9/L, 5) elevated bilirubin (48 µmol/L) with normal liver enzymes.

Empiric treatment with voriconazole and ceftazidime-avibactam was initiated on Day 20. Ultimately, on Day 23, the patient remained unstable on inotropic and vasopressor support. An ECG showed pulseless electrical activity. Despite a 50-minute resuscitation attempt, he could not be revived. The subject died due to MODS.

MO Comment: *I concur with the investigators' assessment that the events of death, myocardial depression, omentitis, intestinal obstruction, febrile convulsions, and MODS are unlikely to be related to C/T. These events are more likely attributable to the worsening of the participant's underlying medical condition, a perforated Meckel's diverticulum, and complications arising from the associated infectious and inflammatory process.*

Serious Adverse Events

Eight subjects experienced SAEs as described in **Table 8-9**. No subject experienced an SAE that was attributed to C/T by the investigator.

Table 8-9. Serious Adverse Events by System Organ Class and Preferred Term (Study P036)

	Ceftolozane/Tazobactam
System Organ Class	**N = 40**
Preferred Term	**n (%)**
Any SAE	8 (20.0)
Cardiac disorders	**2 (5.0)**
Cardiogenic shock	1 (2.5)

Table 8-9. Serious Adverse Events by System Organ Class and Preferred Term (Study P036)

	Ceftolozane/Tazobactam
System Organ Class	**N = 40**
Preferred Term	**n (%)**
Myocardial depression	1 (2.5)
Gastrointestinal disorders	**1 (2.5)**
Intestinal obstruction	1 (2.5)
Omentitis	1 (2.5)
General disorders and administration site conditions	**1 (2.5)**
Multiple organ dysfunction syndrome	1 (2.5)
Infections and infestations	**6 (15.0)**
Bacterial sepsis	1 (2.5)
Candida infection	1 (2.5)
Pneumonia	1 (2.5)
Septic shock	1 (2.5)
Staphylococcal sepsis	1 (2.5)
Urinary tract infection	1 (2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (2.5)**
Benign mediastinal neoplasm	1 (2.5)
Nervous system disorders	**2 (5.0)**
Febrile convulsion	1 (2.5)
Lethargy	1 (2.5)
Product issues	**1 (2.5)**
Device dislocation	1 (2.5)

Source: Table generated by reviewer, OCS Analysis Studio v2.1.6, Safety Explorer.

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

- Participant [redacted] (b) (6) (SAE: Bacterial sepsis, device dislocation)

A 59-day-old female with a complex medical history—including Noonan syndrome, congenital tracheomalacia, ventricular septal defect, and diaphragmatic paralysis—was diagnosed with NP and enrolled in a clinical study. She began a nine-day course of treatment with C/T. During this initial therapy, the patient experienced several complications. On Day 3, her peripherally inserted central catheter broke. On Day 5, she developed a fever, and a sputum culture grew *Klebsiella variicola*. On Day 6, a perianal ulcer was noted, and an abdominal ultrasound revealed increased renal parenchymal echodensity, which was attributed to prior diuretic therapy. The patient's fever resolved by Day 7, and she completed the full course of C/T on Day 9. One day after completing therapy (Day 10), her condition deteriorated. She became pale, tachycardic, and restless and was subsequently diagnosed with bacterial sepsis. Blood and tracheal cultures were positive for *Klebsiella variicola*, the same organism previously identified in her sputum. Treatment was initiated with meropenem and based on susceptibility results, was de-escalated to cefotaxime on Day 15. On Day 17, the patient experienced a separate, non-infectious adverse event when her tracheal cannula became displaced. This led to difficulty with ventilation, hypoxia, and bradycardia. She recovered quickly following mask-bag ventilation and was re-intubated with a nasotracheal device. By Day 21, all signs of infection had resolved, as evidenced by the normalization of laboratory values and the discontinuation of antimicrobial therapy.

- Participant (b) (6) (SAE: Staphylococcus sepsis, lethargy)
  A 246-day-old male with a medical history of encephalopathy and chronic lung disease requiring tracheostomy and gastrostomy tube placement was diagnosed with NP. He was enrolled in a clinical study and began treatment with C/T. During the initial course of therapy, the patient experienced a transient episode of lethargy on Day 2, responding only to painful stimuli. As a precaution, the study drug was temporarily interrupted. An evaluation at that time revealed thrombocytosis (platelet count 617 × 10^9/L), but a brain CT scan showed no new pathological findings. The lethargy resolved by Day 3, and the C/T regimen was resumed. The patient completed the full nine-day course of treatment. However, one day after completing the study treatment (Day 10), the patient's condition worsened significantly. He developed respiratory tract hemorrhage, with bleeding from his mouth, nose, and tracheostomy site, accompanied by leukocytosis (white blood cell count 22.9 × 10^9/L). A subsequent investigation revealed several critical findings:
    - On Day 14, a CT scan of the thorax and abdomen showed esophageal and gastroesophageal mucosal hyperemia.
    - Concurrently, cultures identified new infections: a blood culture was positive for *Staphylococcus warneri*, and a tracheal aspirate grew *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

  Based on these findings, he was diagnosed with staphylococcal sepsis and worsening anemia (hemoglobin 7.8 g/dL). He was treated with intravenous vancomycin and received blood products. The patient experienced a recurrence of lethargy and facial

edema on Day 15, which resolved the following day. The respiratory hemorrhage recurred on Day 23 and was treated with phytomenadione (vitamin K). By Day 24, both the staphylococcal sepsis and the respiratory hemorrhage were noted to be resolving.

- Participant (b) (6) (SAE: Pneumonia)
  A 16-year-old male with a significant medical history, including a gunshot wound resulting in spinal cord and cauda equina injuries, was initially hospitalized for sepsis secondary to left-sided pneumonia and pleural effusion. Approximately three weeks into his hospitalization, he was diagnosed with NP, enrolled in a clinical study, and began treatment with C/T. The patient completed a 15-day course of the study drug. However, two days after treatment completion (Day 17), he was diagnosed with worsening pneumonia. This was accompanied by several significant clinical and laboratory findings: 1) A chest X-ray revealed an acute inflammatory bronchial process, and a subsequent thorax CT scan confirmed a left basal pneumonic process with an associated left pleural effusion; 2) he developed a significant, acute elevation in liver enzymes, with his ALT increasing to 3.39 µkat/L (>3xULN) his AST rising to 2.7 µkat/L (>2xULN). These values represented a marked increase from his baseline levels of ALT 0.92 µkat/L and AST 0.75 µkat/L. In response to his clinical decline, he was started on a broad-spectrum antimicrobial regimen consisting of ceftriaxone, piperacillin-tazobactam, and sulfamethoxazole-trimethoprim. By Day 27 (twelve days after completing the study treatment), the patient's pneumonia and pleural effusion had resolved. His liver enzymes had also significantly improved (ALT 1.26 µkat/L; AST 0.53 µkat/L), and he was subsequently discharged from the hospital.

- Participant (b) (6) (SAE: Candida infection)
  A 9-year-old male with a medical history of scoliosis, cerebral palsy, and epilepsy was diagnosed with NP and enrolled in the clinical study. He successfully completed a nine-day course of treatment with C/T. Two days after completing the study treatment (Day 11), the patient developed a fever of 38 °C. An evaluation revealed the following: 1) blood work showed leukocytosis (white blood cell count: 17.79×10^9/L) and a significantly elevated C-reactive protein (CRP) level of 45.43 mg/L; 2) A blood culture grew *Candida tropicalis.*
  Based on these findings, the patient was diagnosed with candidemia and started on treatment with caspofungin. On Day 19, his therapy was de-escalated from intravenous caspofungin to oral fluconazole. By Day 25, the fungal infection was resolving, and the patient completed his participation in the study.

- Participant (b) (6) (SAE: Benign mediastinal neoplasm, urinary tract infection)
  A 9-year-old female was admitted to the hospital for the surgical resection of a known mediastinal mass. During her hospitalization, she developed NP, was enrolled in the clinical study, and completed a nine-day course of treatment with C/T. Following the completion of the study drug, the patient's clinical course involved two distinct events:

- Surgical Intervention: Six days after finishing the study treatment (Day 15), the patient's primary condition, the benign mediastinal neoplasm, was found to be worsening. She subsequently underwent a mediastinal exploration and successful mass resection.
- New Infection: On Day 24 (fifteen days after study drug completion), she developed new symptoms, including fever, tachycardia, and tachypnea. An investigation led to a diagnosis of a UTI, which was confirmed when a urine culture grew *Proteus mirabilis*. She was promptly started on treatment with cefepime and amikacin.

The UTI responded quickly to therapy. By the following day (Day 25), repeat urine and blood cultures were negative. At this point, with her surgical recovery progressing and the UTI resolving, the patient completed her participation in the study.

***MO Comment**: I agree with the investigators' assessments that the reported SAEs were unlikely to be related to ZERBAXA. The SAE of candidal infection in Participant* (b) (6) *is a known risk associated with the extended use of broad-spectrum antibacterials, which this participant received. The remaining SAEs are related to new bacterial infections that developed after completion of study treatment, progression of underlying disease pathology (mediastinal mass), or device malfunction (dislodgement of tracheal cannula).*

Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations due to adverse effects.

Significant Adverse Events

AEs of anaphylaxis, hypersensitivity, severe skin reaction, *Clostridioides difficile*-associated diarrhea (CDAD), renal impairment, and hemolysis were reviewed, as they are potentially associated with the β-lactam antibacterial drug class. No AEs of anaphylaxis, hypersensitivity, severe skin reaction, CDAD, or hemolysis were reported in study P036.

Most AEs were mild to moderate in severity and occurred across all age groups. All reported severe AE were documented in pediatric participants less than 2 years of age. A total of 5 participants reported 8 severe AEs which included device dislocation, *Staphylococcal* sepsis, lethargy, myocardial depression, intestinal obstruction, MODS, septic shock, and cardiogenic shock. Table 8-10 displays the number of participants who developed AEs by severity and age group in Study P036.

Table 8-10. Participants with Adverse Events (Study P036)

AE Severity	Group 1 12 - <18 y N = 8 n (%)	Group 2 7 - <12 y N = 7 n (%)	Group 3 2 - <7 y N = 8 n (%)	Group 4 3 mo - <2 y N = 10 n (%)	Group 5 Birth - <3 mo N = 7	Total N = 40 n (%)

					n (%)	
Mild	2 (25)	5 (71)	6 (75)	7 (70)	5 (71.4)	25 (62.5)
Moderate	4 (50)	2 (28.6)	1 (12.5)	5 (50)	2 (28.6)	14 (35)
Severe	0	0	0	3 (30)	2 (28.6)	5 (12.5)
Total	4 (50)	5 (71.4)	6 (75)	9 (90)	6 (85.7)	30 (75)

Source: Reviewer Table; adae.xpt; MS Excel
Participants may be counted more than once if they experienced multiple adverse events at different severities.
Abbreviations: N, the total number of participants; n, the number of participants with reported AEs

***MO Comment**: All of the reported severe AEs were also documented as serious adverse events that are described previously. These events were not attributed to C/T and are considered a likely result of the progression of the participants' underlying medical conditions.*

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) that occurred in 5% or greater of patients receiving ZERBAXA in Study P036 are listed in Table 8-11.

Table 8-11. Treatment Emergent Adverse Events Occurring in 5% or Greater of Pediatric Patients Receiving ZERBAXA in Study P036

TEAEs	**HABP/VABP (N=40) n (%)**
Thrombocytosis[1]	7 (17.5)
Pyrexia[2]	6 (15.0)
Alanine aminotransferase increased	5 (12.5)
Anemia	4 (10.0)
Leukopenia[3]	3 (7.5)
Diarrhea	3 (7.5)
Aspartate aminotransferase increased	3 (7.5)
Leukocytosis	2 (5.0)
Intestinal obstruction	2 (5.0)
Nausea	2 (5.0)
Vomiting	2 (5.0)
Withdrawal syndrome	2 (5.0)
Candida infection	2 (5.0)
Croup infection	2 (5.0)
Blood bilirubin increased	2 (5.0)
Hypoalbuminemia	2 (5.0)
Hypokalemia	2 (5.0)
Polyuria	2 (5.0)
Urinary retention	2 (5.0)

[1]Includes platelet count increased

[2]Includes hyperthermia
[3]Includes neutropenia, lymphocyte count decreased
Source: OCS Analysis Studio, Safety Explorer

MO Comment: *The following adverse reactions were reviewed and determined to be unlikely related to ZERBAXA for the reasons specified below:*

- *Croup Infection: This event was considered unrelated to ZERBAXA use, as a plausible biological mechanism is lacking.*
- *Withdrawal Syndrome: This reaction was attributed to the concomitant sedation medications used in the participants' care and was therefore not considered related to ZERBAXA.*
- *Leukocytosis: This finding is a common physiological response to acute bacterial infection and was therefore deemed unlikely to be related to ZERBAXA.*
- *Intestinal Obstruction: This event was identified in two participants, both of whom had predisposing factors for obstruction.*
    - *The first participant ([(b) (6)]) developed the obstruction as a complication of a perforated Meckel's diverticulum.*
    - *The second participant ([(b) (6)]) had a significant medical history that included prior intestinal resection, ileostomy placement, and a history of intestinal obstruction.*

Laboratory Findings

Overall, mean changes from baseline over time for clinical chemistry and hematology parameters were generally small and not clinically significant. There were four participants with notable laboratory changes including leukocytosis, thrombocytosis, elevated transaminases, and elevated bilirubin discussed below. Of note, one participant did meet Hy's Law criteria defined as ALT or AST ≥3x ULN and total bilirubin ≥2x ULN as shown in **Figure 8-1**. This participant is discussed in 8.2.5.1Hepatotoxicity.

The first participant was a 2-year-old female ([(b) (6)]) with trisomy 21 and ulcerative colitis who developed leukocytosis during treatment with C/T for HABP/VABP. Her baseline WBC was 23.8 x 10^9/L and platelet count was 390 x 10^9/L. On Day 5 of treatment, the WBC increased to 65.2 x 10^9/L and her platelet count was 437 x 10^9/L. After completing a 9-day course of C/T, her WBC peaked at 72.99 x 10^9/L and her platelet count increased to 753 x 10^9/L on Day 11. She was also diagnosed with intestinal obstruction on the same day. Her obstruction resolved on Day 16. On Day 25, the WBC count had decreased to 27.3 x 10^9/L, however her platelet count was unchanged (753 x 10^9/L).

MO Comment*: The Applicant attributed this elevation in WBC and platelets to a reactive inflammatory process in the setting of the participant's intestinal obstruction and history of ulcerative colitis. I agree with the Applicant's conclusion that the elevation of WBC and platelets were likely a reactive process secondary to the patient's underlying medical condition and not related to C/T.*

The second participant, a 13-year-old female ([(b) (6)]) with a medical history of cecal necrosis and hemorrhagic peritonitis requiring ileocecal resection and ileostomy, presented at baseline with elevated liver enzymes: AST 1.48 µkat/L, >2x ULN; ALT 0.86 µkat/L. After initiating a 9-day course of C/T, her ALT increased on Day 3 of treatment to 1.43 µkat/L (>3x ULN) while her AST decreased to 0.73 µkat/L (1x ULN) with no other liver function laboratory abnormalities noted. One day after treatment completion (Day 10), her ALT was downtrending to 1.13 µkat/L (2.9X ULN) and her AST had normalized (0.61 µkat/L). At the follow-up visit, 14 days post-treatment, her liver enzymes had normalized (ALT 0.66 µkat/L; AST 0.63 µkat/L).

MO Comment: *The Applicant attributes the participant's elevated AST and ALT to several factors: a recent abdominal surgery (one week prior to treatment), the temporal relationship with the HABP/VABP diagnosis, and the use of concomitant medications known to cause liver enzyme elevations (paracetamol, metamizole, amikacin, and ceftriaxone). I concur with the Applicant's assessment. This conclusion is supported by the clinical data, which show that the participant's ALT levels were decreasing during treatment with C/T and that no other liver function tests became abnormal.*

The third participant, a 7-year-old male ([(b) (6)]) had a medical history of dilated cardiomyopathy, lower gastrointestinal hemorrhage, respiratory failure, cardiac arrest, and acute kidney injury requiring dialysis. He received an eight-day course of C/T. His concomitant medications included meropenem and paracetamol. At baseline, he had mildly elevated liver enzymes (ALT 0.81 µkat/L; AST 1.11 µkat/L). On Day 8 of treatment, his liver enzymes increased to >3x ULN (ALT 2.33 µkat/L; AST 2.7 µkat/L). The following day, the participant completed treatment and his ALT and AST were down-trending (2.17 µkat/L and 1.81 µkat/L, respectively). At the follow-up visit, 14 days post-treatment, his liver enzymes continued to decrease, but had not yet returned to normal (ALT 1.47 µkat/L; AST 0.86 µkat/L). Throughout the treatment and follow-up periods, the participant's bilirubin, alkaline phosphatase, and albumin levels remained within normal limits.

MO Comment: *The Applicant attributes the elevated AST and ALT to the participant's underlying comorbidities and concomitant therapies known to elevate liver enzymes. The Applicant further notes that the AST and ALT levels began to improve while the participant was still receiving C/T. While these risk factors may explain the findings, the temporal relationship between the rise in liver enzymes and the initiation of C/T treatment is difficult to ignore. This association suggests that the study drug may have been a contributing factor to the participant's laboratory abnormalities.*

The final participant, a 3-year-old female ([(b) (6)]), received a nine-day course of C/T. On the last day of treatment, the participant's platelets had increased to 600 x 10^9/L from a baseline of 216 x 10^9/L. At her follow up visit, 14 days post-treatment, her platelet count had normalized to 285 x 10^9/L. Although the participant's liver enzymes and bilirubin were normal during the treatment period, the follow-up visit revealed a newly elevated bilirubin of 12.1

µmol/L (1.5x ULN) and a concurrently elevated direct bilirubin of 2.4 µmol/L.

MO Comment: *The participant was admitted four days prior to study enrollment with first- and second-degree thermal burns on the abdominal wall, back, perineum, and both legs. These burns can cause a reactive thrombocytosis, which is the likely explanation for the participant's elevated platelet count; other complete blood count values remained normal throughout the study period. Regarding the hyperbilirubinemia observed at the follow-up visit, I concur with the Applicant's assessment that it was unlikely to be caused by C/T. This conclusion is supported by the fact that the participant's liver function was normal during treatment, and there was a lack of a temporal relationship between drug administration and the elevated bilirubin. The specific cause of the hyperbilirubinemia is unclear, as limited information was available to investigate potential causes after the participant was discharged from the hospital on Day 9.*

Vital Signs

Vital sign parameters including heart rate, respiratory rate, systolic and diastolic blood pressure, and temperature were assessed at each trial visit. Unless otherwise noted in the participant narratives, there were no significant changes in the vital sign measurements from baseline. The mean changes in vital signs from baseline across the scheduled visits were small.

Electrocardiograms (ECGs)

ECGs were not performed as part of the safety assessment for this study. However, ECG assessments were conducted as part of Study P010 (CXA-PEDS-13-08), a phase 1, non-comparative, open-label study designed to characterize the pharmacokinetics, safety, and tolerability of a single IV dose of C/T in hospitalized pediatric patients. A total of 37 patients (birth to <18 years old) were enrolled. No clinically significant shifts in ECG parameters were observed in the dosage groups.

QT

QT was not measured in study P036. Referring to the original NDA review, C/T was not found to affect cardiac repolarization. This is based on a randomized, positive and placebo-controlled crossover thorough QTc study (CXA-QT-10-02) in which 51 healthy subjects were administered a single therapeutic dose (1.5 g) and a supra-therapeutic dose (4.5 g) of C/T. No significant effects of C/T on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected.

Immunogenicity

Immunogenicity was not assessed in this supplement.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Hepatotoxicity

The study protocol predefined Events of Clinical Interest (ECI) to include elevated liver enzymes or potential drug-induced liver injury (DILI) events that met specific criteria. One subject ((b) (6)) met these criteria for a potential DILI event. This subject is highlighted in **Figure 8-2** as a potential Hy's Law case. However, the investigator assessed the event as not being drug-related.

Subject (b) (6)
A 22-day-old male with a history of bilateral ureterohydronephrosis and neonatal jaundice was hospitalized and diagnosed with NP. At baseline, he already presented with elevated AST (94.6 IU/L), total bilirubin (6.8 mg/dL), and direct bilirubin (2.46 mg/dL). He was enrolled in a clinical study and began treatment with C/T, administered concomitantly with meropenem.

During the course of treatment, the patient's liver function markers continued to rise. On Day 3, his ALT increased to 68.3 IU/L, while his AST and bilirubin rose to 132.4 IU/L and 7.01 mg/dL, respectively. A chest X-ray on the same day revealed a left-sided pneumothorax. By Day 7, his alkaline phosphatase (ALP) had increased to 443.2 IU/L, and his total bilirubin had risen further to 9.13 mg/dL.

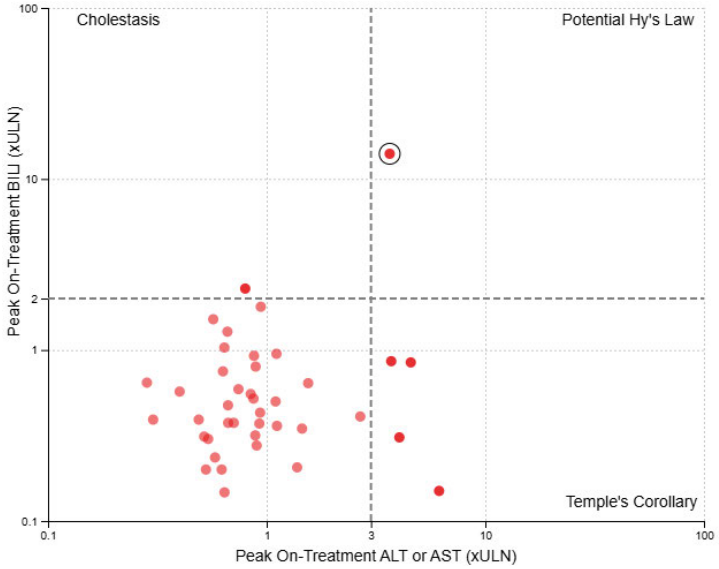
The patient completed the course of C/T on Day 9. The following day, his hyperbilirubinemia and liver enzyme elevation persisted (ALT 72.1 IU/L, AST 133.2 IU/L, bilirubin 9.73 mg/dL, and ALP 508.7 IU/L). An investigation into his underlying urological condition via retrograde cystography confirmed grade III left-sided and grade I right-sided hydronephrosis. To address the obstruction, he underwent a Sober ureterocutaneostomy and was started on treatment with ceftazidime-avibactam.

On Day 23 (14 days after completing study treatment), the patient's hepatic enzymes showed a worsening elevation (ALT 156.2 IU/L; AST 289 IU/L), although his bilirubin had decreased to 5.99 mg/dL. This was clinically attributed to his underlying neonatal jaundice and urological pathology, as there were no new clinical manifestations of liver dysfunction. He was discharged home with a plan for future surgical intervention. By Day 68, the elevation in his hepatic enzymes was resolving and his bilirubin had normalized (ALT 132.3 IU/L, AST 125.3 IU/L, and bilirubin 1.28 mg/dL).

MO Comment: *Of note, the patient had elevated AST, total bilirubin, and direct bilirubin at baseline prior to starting ZERBAXA. Although obstructive uropathy can be associated with indirect hyperbilirubinemia, this condition is typically caused by secondary factors such as infection (e.g., urinary tract infection) or feeding difficulties that lead to dehydration and increased enterohepatic circulation of bilirubin. The investigator attributed the participant's elevated liver enzymes and bilirubin to the underlying urologic pathology and neonatal jaundice,*

which is possible. Additionally, a bacterial infection could have contributed to these laboratory findings, as infections can increase bilirubin production, impair its hepatic conjugation, and increase its enterohepatic circulation.

Figure 8-2. Evaluation of Drug-Induced Serious Hepatotoxicity Plot in Study P036



Source: Graph generated by the reviewer, OCS Analysis Studio v2., Hepatic Explorer.
Filters: None.
Note: Hepatotoxicity Candidates: ALT or AST >= 3*ULN; BILI >= 2*ULN (0-30 days forward); ALP < 2*ULN (0-999 days backward).
Note: Missing ULN values are imputed as the weighted mean of the present ULN values per lab test code per subject.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal.

8.2.5.2. Ceftolozane/Tazobactam Dosage Increase

The efficacy of ZERBAXA for treating HABP/VABP in pediatric patients was extrapolated from data in adult patients with the same condition. During the review, the clinical pharmacology team determined from clinical pharmacokinetic (PK) data that drug exposures were substantially lower in pediatric patients 2 years of age and older—specifically, 1.6-fold lower for ceftolozane and 1.8-fold lower for tazobactam median exposures (measured as AUC_{0-8}) compared to respective adult exposures. To address this discrepancy, additional PK modeling and simulations were performed. The modeling and simulation findings supported an adjustment of a 25% dose increase to ZERBAXA 75 mg/kg (50 mg/kg of ceftolozane and 25 mg/kg of tazobactam) given every 8 hours, combined with an extended infusion time of two hours in pediatric HABP/VABP patients aged 2 years and older. This revised approach is

projected to achieve pediatric exposure measures (AUC_{0-8} and Cmax values for both drugs) comparable to those observed in adult HABP/VABP patients.

Due to this adjusted change in dosing, the recommended dosage of ZERBAXA for pediatric patients from 32 weeks gestational age to less than 2 years is 60 mg/kg (40 mg/kg ceftolozane and 20 mg/kg tazobactam) given every 8 hours over a 2 hour infusion. The infusion time was adjusted to mitigate potential medication errors, while still maintaining AUC_{0-8}. For pediatric patients 2 years of age and older, the recommended dosage of ZERBAXA is 75 mg/kg (50 mg/kg ceftolozane and 25 mg/kg tazobactam) given every 8 hours over a 2 hour infusion. For further details on the data extrapolation and dosing modification, refer to section 6.2.

The proposed dose increase is also supported by the well-established safety profile of beta-lactams and beta-lactamase inhibitors. This drug class has a wide therapeutic index because it selectively targets bacterial cell wall synthesis, a mechanism absent in human cells, which minimizes off-target effects. Based on the pediatric PK data from the study, modeling indicates that the increased dose of C/T can be administered without exceeding the 95th percentile of adult Cmax and AUC values, thus remaining within the drug's established safety margins. Furthermore, prolonging the infusion time from one to two hours helps mitigate potential concentration-dependent toxicities while ensuring efficacy by maximizing the time that drug concentrations remain above the minimum inhibitory concentration (MIC).

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

Clinical outcome of Study P036 was assessed by clinician as described in Section 8.1 of this review. No clinical outcome assessments were performed for this study.

8.2.7. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were not conducted due to a small number of participants in demographic subgroups.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new carcinogenicity studies were submitted with this application. The relatively short duration of therapy and treatment follow-up and non-comparative study design in Study P036 precludes a meaningful event of oncologic events. For the original assessment, refer to Section 4.3 of the clinical review of the original NDA.

Previously, ceftolozane and tazobactam showed no mutagenic potential in a series of in vivo and in vitro genetic toxicity assays, and no safety signals related to human carcinogenicity have been identified. This is consistent with the intended use of antibacterial drugs, which are

generally administered as a single, short-term course of treatment for an acute illness; therefore, prolonged exposure is not anticipated.

Human Reproduction and Pregnancy

No new information regarding human reproduction and pregnancy was submitted. The safety study of ZERBAXA in pediatric patients with HABP/VABP excluded patients who were pregnant, attempting to conceive, or lactating.

Pediatrics and Assessment of Effects on Growth

No assessment of effects on growth were made. The participants were not followed long-term to determine the 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

ZERBAXA and its components are not known to be associated with abuse, withdrawal or rebound effects. No overdoses occurred in the pediatric study P036.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Since the approval of ZERBAXA, the Applicant has submitted routine pharmacovigilance reports, including annual reports and Periodic Adverse Drug Experience Reports (PADERs). Seizures have been reported in patients receiving ZERBAXA. Most reports occurred in critically ill patients with multiple risk factors for seizures, including renal impairment, sepsis, and metabolic abnormalities. A causal relationship to ZERBAXA has not been established. No cases were identified via FDA MedWatch and there were no cases of seizures identified in this review.

A review of postmarketing safety reports from the FDA Adverse Event Reporting System (FAERS) between 2020 and 2025 identified five pediatric cases involving off-label use of C/T. The patients, who ranged in age from 5 months to 17 years, were being treated for various serious infections, including skin and soft tissue infection, typhlitis, hospital-acquired pneumonia, and CF exacerbation. The adverse events reported in these cases were thrombocytosis, pathogen resistance, and neutropenia. Thrombocytosis is a known adverse reaction that is already included in the product's labeling. Pathogen resistance to the drug was observed to have developed in four of the five patients after treatment. The single case of neutropenia was reported in a patient with metastatic B-cell lymphoma who was also receiving ganciclovir. An evaluation of the relationship between the drug and this adverse event was complicated by the patient's underlying disease and the concomitant use of ganciclovir, which is also known to cause neutropenia, making it difficult to determine causality.

Expectations on Safety in the Postmarket Setting

ZERBAXA is currently on the market and there are no expectations for the development of new safety issues.

8.2.10. Integrated Assessment of Safety

A total of 210 pediatric participants, from birth (>32 weeks GA and ≥7 days postnatal) to younger than 18 years, were exposed to ZERBAXA across three studies for cUTI, cIAI, and HABP/VABP. In the HABP/VABP study (P036), three deaths occurred, all of which were attributed to the progression of the underlying disease and considered unrelated to ZERBAXA. A total of eight serious adverse events (SAEs) were reported, all determined to be unrelated to the study drug, and there were no discontinuations due to adverse events.

No new safety signals were identified, and adverse events were generally mild to moderate in intensity. Across all pediatric studies, the most common AEs included thrombocytosis, pyrexia, diarrhea, leukopenia, abdominal pain, and increased ALT and AST. Elevations in liver enzymes, a known adverse reaction already described in the ZERBAXA prescribing information, were observed in a few participants. Notably, there were no cases of anaphylaxis or *Clostridioides difficile*-associated diarrhea. Overall, the safety profile of ZERBAXA in pediatric patients with HABP/VABP appears consistent with the profile observed in pediatric patients with cUTI and cIAI as well as adult patients with HABP/VABP. Please refer to the original review of sNDA 011 and 012 for additional safety information on the use of ZERBAXA in pediatric patients.

8.3. Statistical Issues

Study P036 was a descriptive study with a limited number of participants and without a control group, with the primary aim to evaluate PK, safety, and tolerability of ZERBAXA in pediatric patients with HABP/VABP. This study was not adequately powered for hypothesis testing. Therefore, statistical inferences could not be drawn.

8.4. Conclusions and Recommendations

The reviewers conclude that the Applicant has provided sufficient evidence to support the approval of ZERBAXA for the treatment of hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) in pediatric patients from at least 32 weeks gestational age to younger than 18 years old.

The extrapolation of ZERBAXA's efficacy from adults to this pediatric population is supported by Study P036 and is based on similarities in pharmacokinetics, disease pathophysiology, and microbiology between the two groups. Regarding safety, no new signals were identified in Study P036. The overall safety profile in pediatric patients with HABP/VABP is consistent with that observed in other populations treated with ZERBAXA, including pediatric patients with cIAI and cUTI and adult patients with HABP/VABP.

Finally, this application fulfills the Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR) 3637-1.

9 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting convened for this sNDA.

10 Pediatrics

This submission evaluates the safety and effectiveness of ZERBAXA for treating complicated HABP/VABP in children ranging from birth to those under 18 years of age. The FDA's Pediatric Review Committee (PeRC) provided consultation and confirmed that this application satisfies the requirements of PREA PMR 3637-1. No additional postmarketing requirements remain pending. The Division of Pediatric and Maternal Health (DPMH) was engaged to support the evaluation of pediatric-specific labeling terminology within the Prescribing Information. DPMH representatives attended relevant team discussions regarding the application and contributed to labeling recommendations. Refer to the DPMH review in DARRTS dated 5/8/2026 for additional details.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved). The finalized PI was compared to the currently approved PI and the Applicant's proposed labeling submitted and received on November 12, 2025 (see **Table 11-1** below).

The PI was reviewed to ensure that the PI meets regulatory and statutory requirements; is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner. Division of Pediatric and Maternal Health (DPMH) was consulted and contributed to the recommendations on the pediatric dosing information. Refer to the DPMH review in DARRTS dated 5/8/2026 for additional details.

The Highlights (HL) section of the PI was updated with major changes made to sections 1 (Indications and Usage), 2 (Dosage and Administration), 6 (Adverse Reactions), and subsection 8.4 (Pediatric Use) of the full prescribing information (FPI) as described in **Table 11-1** below.

Table 11-1. Summary of Key Changes to the Prescribing Information

Full Prescribing Information (FPI) Sections	Applicant Proposed Labeling	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI) Compared to the last Approved PI and the Applicant's PI submitted on November 12, 2025
1 INDICATIONS AND USAGE	In subsection 1.3 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia, defined pediatric patients as (b) (4)	In subsection 1.3 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia, revised age range of pediatric patients to "at least 32 weeks gestational age." In subsections 1.1 Complicated Intra-abdominal Infections and 1.2 Complicated Urinary Tract Infections, Including Pyelonephritis, changed the currently approved pediatric age range to read as "at least 32 weeks

		gestational age" instead of (b) (4) ." Refer to Section 6.2 of the Unireview for additional details.
2 DOSAGE AND ADMINISTRATION	- In subsection 2.1 Recommended Dosage in Adult Patients, included creatinine clearance to define adult patients with normal renal function. - In subsection 2.2 Recommended Dosage in Pediatric Patients (b) (4) , included (b) (4) - In subsection 2.3 Dosage Adjustments in Adult Patients with Renal Impairment, defined creatinine clearance 50 mL/min or less as renal impairment in adult patients. - In subsection 2.4, Dosage Adjustments in Pediatric Patients with Renal Impairment, defined eGFR 50 mL/min/1.73m^2 or less as renal impairment in pediatric patients. - In subsection 2.2, Table 2 Dosage of ZERBAXA by infection in Pediatric Patients (birth to less 18 years of age) with eGFR greater than 50 mL/min/1.73m2, was updated to include pediatric dosing for HABP/VABP with ZERBAXA (b) (4)	- In subsection 2.1 Recommended Dosage in Adult Patients removed the creatinine clearance definition of adult patients with normal kidney function and added a note that dosing for adult patients with renal impairment is provided in subsection 2.3 Recommended Dosage in Adult Patients with Renal Impairment. - In subsection 2.2 Recommended Dosage in Pediatric Patients (at least 32 weeks gestational age), removed the (b) (4) for pediatric patients and included a statement that dosing for pediatric patients with renal impairment is provided in subsection 2.4 Recommended Dosage in Pediatric Patients with Renal Impairment. - Additionally, since (b) (4) criteria is removed in subsection 2.2, deleted the statement (b) (4) .” - In subsection 2.2, modified Table 2 Recommended Dosage of ZERBAXA by Infection in Pediatric Patients (at least 32 weeks gestational age) to include the age range for dosing, starting from at least 32 weeks gestational age. In Table 2, differentiated HABP/VABP dosing in pediatric patients: those under 2 years of age receive ZERBAXA 60 mg/kg

	[redacted] (b) (4) . Also revised eGFR to be calculated using [redacted] (b) (4) . - In subsection 2.4 Dosage Adjustment in Pediatric Patients with Renal Impairment, updated to include dose adjustment is required in pediatric patients (2 to less than 18 years of age) with eGFR 50 mL/min/1.73m^2 or less. Added Table 4 Recommended Dosage Requirements for ZERBAXA in Pediatric Patients 2 to 18 years of age with Renal Impairment to guide dose adjustment for cIAI, cUTI, and HABP/VABP based on eGFR using [redacted] (b) (4) .	administered over a 2-hour infusion, while those 2 years of age and older receive the modified dose of ZERBAXA 75 mg/kg administered over a 2-hour infusion. Refer to Section 6.2 of the Unireview for additional details. - Expanded Table 3 Recommended Dosage of ZERBAXA in Adult Patients with Renal Impairment in subsection 2.3 of the PI to include dosing for estimated CrCl of 51 to less than 90 mL/min. In Table 3, added a row to indicate that dosage is not established for adult patients with CrCl less than 15 mL/min and not receiving IHD. - Expanded Table 4 Recommended Dosage Regimens for ZERBAXA in Pediatric Patients 2 years of age and older with Renal Impairment in section 2.4 of the PI to included estimated GFR of less than 90 mL/min/1.73m^2 and lower and adjusted dosing recommendations for pediatric patients with renal impairment diagnosed with HABP/VABP. In Table 4, modified dose for HABP/VABP and added a row to indicate that dosage is not established for pediatric patients with eGFR less than 15 mL/min/1.73m^2 and not receiving IHD. Refer to Section 6.2 of the Unireview and the DPMH review (in DARRTS dated 5/8/2026) for additional details. - Removed the footnotes from Table 2 and Table 4 that referenced the [redacted] (b) (4) and revised the footnote in Table 4 to state “estimate eGFR using an

		equation validated in pediatric patients in the approved age range" as per the Labeling recommendations in the FDA Draft Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products-Content and Format (January 2023).
3 DOSAGE FORMS AND STRENGTHS	N/A	N/A
4 CONTRAINDICATIONS	N/A	N/A
5 WARNINGS AND PRECAUTIONS	N/A	N/A
6 ADVERSE REACTIONS	- In Subsection 6.1 Clinical Trials Experience, included short paragraph on the adverse reactions (AR) identified in the pediatric HABP/VABP trial.	- In subsection 6.1 Clinical Trials Experience, expanded the description of the pediatric HABP/VABP clinical trial and included the most common ARs that occurred in greater than 7% of the pediatric patients. Refer to Section 8.2 of the Unireview for additional details.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	- In subsection 8.4 Pediatric Use: - Added HABP/VABP to pediatric use statement at the beginning of subsection 8.4. - Included a statement for dosage adjustment in pediatric patients with renal impairment 2 years of age and older. - Updated a statement to indicate that there is insufficient information to recommend dosage adjustment for pediatric patients younger than 2 years of age with renal impairment. - In subsection 8.6 Renal	- In subsection 8.4 Pediatric Use: - Defined the age of pediatric patients to include those at least 32 weeks gestational age and older for the HABP/VABP indication as well as the cIAI and cUTI indications. Refer to Section 6.2 of the Unireview for additional details. - Added a statement noting that the safety profile of ZERBAXA in pediatric patients was similar to adults with cIAI, cUTI and HABP/VABP. Refer to Section 8.2 of the Unireview for additional details. - Included a statement noting that safety and effectiveness of ZERBAXA has not been established for pediatric patients

	Impairment, updated to include that (b) (4) [redacted].	younger than 32 weeks gestational age and that dosing is not recommended in pediatric patients with renal impairment who are younger than 2 years of age. Refer to Section 6.2 of the Unireview for additional details. - In subsection 8.6 Renal Impairment: - Removed (b) (4) [redacted] of renal impairment and redefined renal impairment based on eGFR for pediatric patients and CrCl for adult patients. - Included a statement that dosing is not established for adult and pediatric patients with a CrCl <15 mL/min or eGFR <15 mL/min/1.73m^2 who are not receiving IHD.
12 CLINICAL PHARMACOLOGY	- In subsection 12.3 Pharmacokinetics, under the Pediatric patients with HABP/VABP subheading, updated to include PK information from the pediatric HABP/VABP clinical study - Added Table 13 "Steady-State Plasma Population Pharmacokinetic Parameters (Mean and SD) of ZERBAXA (ceftolozane and tazobactam) in Pediatric HABP/VABP Patients**"** to represent the mean population pharmacokinetic parameters of ZERBAXA at the dose studied in Study P036.	- Updated subsection 12.3 Pharmacokinetics under "Adult Patients with Renal Impairment" subheading: - Changed ESRD to CrCl less than 15 mL/min and HD to Intermittent hemodialysis so that the statement reads as "In subjects with CrCl less than 15 mL/min on intermittent hemodialysis, approximately two-thirds of ZERBAXA dose is removed." - Added statement that dosage is not established in adult patients with CrCl less than 15 mL/min who are not receiving IHD. - Removed statement about ESRD and HD dosage recommendations because this clinical recommendation is appropriately located in the Dosage and Administration section under subsection 2.3. Therefore, a cross-

		reference to subsection 2.3 was included. This is consistent with the labeling recommendations in the FDA Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products-Content and Format (December 2016). - In subsection 12.3 Pharmacokinetics under "Pediatric Patients with cIAI and cUTI" subheading, included the age range for PK data in pediatric patients with cIAI and cUTI. - In subsection 12.3 Pharmacokinetics under "Pediatric Patient with HABP/VABP" updated information to include the age ranges of pediatric patients enrolled in the trial and removed the statement about population PK analyses and target attainment in pediatric patients with HABP/VABP compared to adults with HABP/VABP. - Modified Table 13 "Steady-State Plasma Population Pharmacokinetic Parameters (Mean and SD) of ZERBAXA (ceftolozane and tazobactam) in Pediatric HABP/VABP Patients" to represent the mean population pharmacokinetic parameters of ZERBAXA at the recommended dose (not at the studied dose in Study P036). - Included a footnote in Table 13 to note that pediatric patients as young as 35 weeks post-menstrual age were enrolled. - Updated the text under the "Pediatric Patients with Renal Impairment" subheading to remove

		[redacted], as well as [redacted]. - Redefined renal impairment in pediatric patients aged 2 years and older based on eGFR values (i.e., less than 90 mL/min/1.73m^2 or eGFR less than 15 mL/min/1.73m^2 and receiving IHD). This is because categorizing eGFR into mild, moderate, or severe categories may vary for prescribers based on eGFR cutoffs. Refer to Section 6.2 of the Unireview for additional details. - In subsection 12.4 Microbiology, under the Resistance subheading, updated from Enterobacteriaceae to Enterobacterales to reflect the current taxonomy. See additional details in the section 14 Clinical studies of this table below.
14 CLINICAL STUDIES	N/A	- Included National Clinical Trial (NCT) numbers for the clinical trials for cIAI, cUTI and HABP/VABP described in Section 14 CLINICAL STUDIES. - Included age range enrollment criteria in description of pediatric clinical trials for cIAI, cUTI and HABP/VABP. - Table 21, Day 28 All-cause Mortality and Clinical Cure Rates at TOC by Baseline Pathogen from a Phase 3 Study of Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (Trial 3; mITT population) was updated from Enterobacteriaceae to Enterobacterales to reflect the current taxonomy. This is because Enterobacterales is now an order, and *P. mirabilis* and *S. marcescens* are not included in the Enterobacteriaceae family.

[1] For purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Approved Labeling Types
Upon approval of this efficacy supplement (sNDA 206829/S023), the Prescribing Information will be the only new FDA-approved labeling document.

12 Risk Evaluation and Mitigation Strategies (REMS)

REMS is not warranted. Currently, available evidence does not suggest that the safety concerns related to ZERBAXA administration in children are greater than those observed with other antibacterial medications in the cephalosporin class. These potential risks can be adequately addressed through the product labeling for ZERBAXA, consistent with the approach used for the adult patient population.

13 Postmarketing Requirements and Commitment

Please see Section 3 Regulatory Background for details regarding PMR 3637-1. This submission fulfills PMR 3637-1.

14 Designated Signatory Authority Comments

I agree with the conclusions of this review and with approval of this efficacy supplement.

15 Appendices

15.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study P036

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 84		
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 reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

15.2.1. Clinical Pharmacology Study

P036 MK7625A (P036)

This was a phase 1, open-label, non-comparative study evaluating the safety, tolerability, and PK of C/T in pediatric participants from birth (≥32-week GA and at least 7 days postnatal age) to <18 years of age with HABP/VABP receiving concomitant standard-of-care antibacterial therapy. Participants with eGFR <50 ml/min/1.73m^2 (3 months and over) and <20 ml/min/1.73m^2 (birth to <3 months) or required hemodialysis were excluded. The eGFR were determined based on the revised Schwartz equation. A total of 40 participants were enrolled and received C/T as a 1 hour IV infusion every 8 hours for 8 to 14 days, stratified by age; participants 12 to <18 years received a fixed dose of 3 g C/T and participants <12 years received 60 mg/kg (maximum 3 g). Sparse PK samples were collected on Day 3 after at least 6 doses at three timepoints: end of infusion, 4 to 5 hours post-infusion, and 7 to 8 hours post-infusion. Of the 40 enrolled participants, 39 were included in the PK analysis population as one participant's samples were lost during delivery to the central laboratory. C/T plasma concentrations were analyzed with a validated bioanalytical LC/MS-MS assay that was previously reviewed and deemed appropriate by the Clinical Pharmacology Review team in 2022.[9] Performance during P036 sample analysis met the 2022 ICH M10 guidance.

Overall, the post hoc PK parameter estimates of the 39 pediatric patients that were determined from population PK model are summarized below in **Table 15-1.** The simulated PK parameter estimates for the finally agreed upon dosage in **Table 6-1** are provided in **Table 15-2** below.

Table 15-1. Post Hoc Mean (SD) C/T Pharmacokinetic Parameters in Study P036 Pediatric HABP/VABP Patients

Patient Characteristics	Group 1 (12 to <18 years)	Group 2 (7 to <12 years)	Group 3 (2 to <7 years)	Group 4 (3 months to <2 years)	Group 5 (Birth to <3 months)*
	N=8	N=7	N=7	N=10	N=7
Ceftolozane					
C_{max} (µg/mL)	115.5 (23)	106.9 (15)	92.9 (12)	100.4 (17)	105.6 (14)
AUC_{0-8} (µg•h/mL)	243 (50)	213 (47)	176 (34)	258 (103)	350 (101)
Clearance (L/h)	8.53 (1.66)	5.92 (2.68)	3.09 (0.84)	1.24 (0.65)	0.44 (0.17)
V_{ss} (L)	17.9 (3.8)	11.4 (6.0)	4.9 (0.7)	2.8 (1.0)	1.7 (0.5)
Tazobactam					
C_{max} (µg/mL)	24.7 (5)	25.6 (7)	20.5 (5)	25.5 (8)	28.9 (5)
AUC_{0-8} (µg•h/mL)	30 (6)	34 (13)	26 (7)	41 (24)	55 (27)
Clearance (L/h)	34.09 (6.09)	19.17 (8.05)	11.26 (4.37)	4.39 (2.76)	1.50 (0.62)
V_{ss} (L)	27.4 (7.3)	18.1 (9.7)	7.7 (1.6)	4.5 (1.6)	2.5 (0.7)

Source: Table 2.7.2-pedsnp: summary-clin-pharm-pedsnp on 11/20/2025
AUC_{0-8}, area under the curve in the dosing interval 0 to 8 hours at steady-state; C_{max}, maximum serum concentration; V_{SS}, steady-state volume of distribution.
*Includes pediatric patients at least 32 weeks gestational age and at least 7 days postnatal age.

Table 15-2. Simulated Mean (SD) C/T Pharmacokinetic Parameters at Recommended Dosage by Age Group†

Patient Characteristics	Group 1 (12 to <18 years)	Group 2 (7 to <12 years)	Group 3 (2 to <7 years)	Group 4 (3 months to <2 years)	Group 5 (Birth to <3 months)*
	N=8	N=7	N=7	N=10	N=7
Ceftolozane					
C_{max} (µg/mL)	77.6 (12)	86.0 (17)	78.2 (11)	73.9 (16)	83.7 (14)
AUC_{0-8} (µg•h/mL)	235 (39)	251 (62)	220 (43)	258 (103)	350 (101)
$t_{1/2}$ (hr)	1.8 (0.2)	1.7 (0.2)	1.5 (0.3)	2.2 (0.8)	3.1 (0.9)
Clearance (L/h)	8.53 (1.66)	5.92 (2.68)	3.10 (0.84)	1.24 (0.65)	0.44 (0.17)
V_{ss} (L)	17.9 (3.8)	11.4 (6.0)	4.9 (0.7)	2.8 (1.0)	1.7 (0.5)
Tazobactam					
C_{max} (µg/mL)	13.1 (2)	17.2 (6)	14.2 (4)	15.6 (6)	18.8 (5)
AUC_{0-8} (µg•h/mL)	29.3 (5)	40.5 (17)	31.8 (9)	41.1 (24)	55.2 (27)
$t_{1/2}$ (hr)	1.7 (0.1)	1.7 (0.3)	1.4 (0.1)	1.7 (0.5)	2.1 (0.7)
Clearance (L/h)	34.09 (6.09)	19.17 (8.05)	11.26 (4.37)	4.39 (2.76)	1.50 (0.62)
V_{ss} (L)	27.4 (7.3)	18.1 (9.7)	7.7 (1.6)	4.5 (1.6)	2.5 (0.7)

Source: Information request response dated 04/29/2026
C_{max}, maximum serum concentration; AUC_{0-8}, area under the curve in the dosing interval 0 to 8 hours at steady-state; $t_{1/2}$, terminal half-life; V_{SS}, steady-state volume of distribution.
*Includes pediatric patients at least 35 weeks post-menstrual age.
† Pediatrics 2 years and older with C/T 75 mg/kg dose (C:50 mg/kg and T:25 mg/kg) or 3 g max dose (C:2 g and T: 1 g) every 8 hours via 2-hour infusion; birth to <2 years with C/T 60 mg/kg dose (C:40 mg/kg and T:20 mg/kg) every 8 hours via 2-hour infusion

15.2.2. Ceftolozane/Tazobactam Joint Probability of Target Attainment Findings in Pediatrics at the Susceptibility Breakpoint MICs

HABP/VABP

- The Applicant's original PTA analyses used a (b) (4)% fT>MIC target for ceftolozane ((b) (4)), which was utilized to support cUTI and cIAI adult dosage recommendations. However, for HABP/VABP adult dosage, a more conservative 40% fT>MIC target (2-log kill) was utilized to support adult HABP/VABP indication approval in 2019 (NDA 206829/S-008).[11] Therefore, the Agency requested updated PTA analyses using the 40% fT>MIC target, which the Applicant provided. All the aforementioned PTA findings in **Sections 6.2.1 and 15.2.2** for HABP/VABP use the 40% fT>MIC target for ceftolozane and 20% fT>concentration threshold of 1 µg/mL for tazobactam.
- ELF is the relevant infection site matrix for the HABP/VABP indication. While direct pediatric ELF data were not collected, the use of adult ELF penetration ratios of approximately 50% for ceftolozane and 62% for tazobactam in pediatric extrapolations is an acceptable approach. This extrapolation is supported by physiological, physicochemical, and protein-binding considerations that are consistent across age groups, as well as an established regulatory precedent and published literature of another cephalosporin.[12]
- Plasma PTAs at the susceptibility breakpoint MICs (Enterobacterales MIC=2 µg/mL; *P. aeruginosa* MIC=4 µg/mL) were ≥90% across all pediatric age groups with the recommended dosage and provided additional supportive evidence (data not shown).
- Joint ELF PTAs ≥90% were achieved at susceptibility breakpoint MICs across all renal categories and age groups with the recommended dosages **(Table 6-6**).

cUTI/cIAI

- Compared to the prior submission, joint PTAs for cUTI/cIAI pediatric patients with eGFR > 50 mL/min/1.73m^2 are substantially lower in the current analysis (50-65% [**Table 15-3 and Table 15-4]** vs. >85% [in the 2022 pediatric cUTI/cIAI approval][9]**)**. The lower joint PTAs for cUTI/cIAI relative to the prior submission are driven primarily by lower predicted tazobactam exposures in the updated population PK model. In the updated model, the relationship between renal function and tazobactam clearance was derived from adult data, including HABP/VABP patients;[13] this relationship predicts a steeper increase in tazobactam clearance with improving renal function than was estimated from the original pediatric cUTI/cIAI data.[14] Applying this relationship to the cUTI/cIAI population results in lower predicted tazobactam exposures compared to the prior

[11] NDA206829-Suppl 8. Unireview; DARRTS date 5/31/2019
[12] Dong YN, Wang YK, Li Q, et al. Br J Clin Pharmacol. 2023;89:1491–1494.
[13] Applicant's PopPK Report 08wwfz date 11/11/2025 (link)
[14] Applicant's PopPK Report 05qwch date 5/21/2021 (link).

model (up to 32% lower for cIAI patients 6 to <12 years),[13] and consequently contributes to the lower joint PTAs observed in the current analysis.

- Tazobactam exposures were already the limiting factor for PTA results in the prior submission— the only subgroup below 90% joint PTA was cUTI patients 7 to <12 years at 86.7%, driven entirely by tazobactam exposures (since ceftolozane PTAs were 100%).[9] In the current analysis, for cIAI with eGFR > 50 mL/min/1.73m^2, both ceftolozane and tazobactam contribute to lower joint PTAs (**Table 15-4)**; however, for all renally impaired subgroups, tazobactam is the sole driver for lower PTAs (**Table 15-3 and Table 15-4**). The updated model may be underpredicting tazobactam exposures, and the true joint PTAs may be closer to the previously accepted thresholds. The proposed C/T dosages are considered acceptable for eGFR ≤ 50 mL/min/1.73m^2 based on the following considerations:
    - Simulated C/T exposures in pediatric cUTI/cIAI patients with eGFR ≤50 mL/min/1.73m^2 were comparable to or higher than those in pediatric patients with normal renal function receiving the approved eGFR >50 mL/min/1.73m^2 dosage evaluated in P034 and P035 (**Table 6-8)**, supporting effectiveness. While ceftolozane and tazobactam AUC0-8 values were lower than adult cUTI and cIAI patients with normal renal function (CrCL >50 mL/min) for the eGFR 30–50 and 15–<30 mL/min/1.73m^2 categories (**Table 6-7**), the pediatric normal renal function reference is the more appropriate comparator given that the pediatric dosing was established relative to this population.
    - Individual ceftolozane PTAs are ≥90% across all renally impaired subgroups for both cUTI and cIAI (**Table 15-3 and Table 15-4**).
    - Joint PTAs are substantially higher in pediatrics with eGFR ≤50 mL/min/1.73m^2 relative to the eGFR >50 mL/min/1.73m^2 group despite possible tazobactam underprediction.
    - The proportional dosing adjustment framework across renal impairment categories is consistent with the approved adult approach.

Table 15-3. Steady-State Ceftolozane and Joint C/T Plasma PTA at the *P. aeruginosa* Breakpoint (MIC = 4 µg/mL) in Virtual Pediatric cUTI Patients by Renal Function Category

Dosage (1 h infusion)	eGFR ml/min/1.73m^2	2 to <6 y		6 to <12 y		12 to <18y	
		Ceftolozane	Joint	Ceftolozane	Joint	Ceftolozane	Joint
30 mg/kg q8h	>50	90.5%	50%	92%	53%	94%	57%
15 mg/kg q8h	30 to 50	100%	85%	100%	89%	100%	88%
7.5 mg/kg q8h	15 to <30	100%	83%	100%	88%	100%	85%
LD: 15 mg/kg x 1 MD: 3 mg/kg q8h	Receiving IHD	100%	87%	100%	92%	100%	97%

Adapted from Report 08wwfz.pdf-Tables 78-81, 86-89
Note: PK-PD target for ceftolozane is 30%fT>MIC and tazobactam is 20%fT>MIC; LD, loading dose; MD, maintenance dose, IHD-intermittent hemodialysis

Table 15-4 Steady-State Ceftolozane and Joint C/T Plasma PTA at the *P. aeruginosa* Breakpoint (MIC = 4 µg/mL) in Virtual Pediatric cIAI Patients by Renal Function Category

Dosage (1 h infusion)	eGFR ml/min/1.73m^2	2 to <6 y		6 to <12 y		12 to <18y	
		Ceftolozane	Joint	Ceftolozane	Joint	Ceftolozane	Joint
30 mg/kg q8h	> 50	83%	58%	84%	60%	86%	65%
15 mg/kg q8h	30 to 50	100%	90%	100%	93%	100%	93%
7.5 mg/kg q8h	15 to <30	99%	87%	99%	90%	99%	89%
LD: 15 mg/kg x 1 MD: 3 mg/kg q8h	Receiving IHD	100%	87%	100%	92%	100%	98%

Adapted from Report 08wwfz.pdf-Tables 90-93, 98-101
Note: PK-PD target for ceftolozane is 30%fT>MIC and tazobactam is 20%fT>MIC; LD, loading dose; MD, maintenance dose, IHD-intermittent hemodialysis.

15.2.3. Pharmacometrics

The developed population PK models were considered acceptable for describing ceftolozane and tazobactam concentrations in pediatric patients (birth to <18 years) with nosocomial pneumonia (NP), complicated urinary tract infections (cUTI) or complicated intra-abdominal infections (cIAI). The PK models were used to predict exposure metrics and support dosage recommendation in pediatric patients from birth to <18 years with normal or impaired renal function. The PK modelling was utilized to support the current submission as outlined below:

Table 15-5. Utility of the Population PK Modeling

Utility of the final model	Reviewer's Comments
• The PK models for ceftolozane and tazobactam consisted of 2-compartment disposition models with a zero-order input (IV infusion) and linear elimination from the central compartment. The PK models accounted for the effects of renal maturation and renal function (eGFR) on clearance (CL). The effects of infection type (cUTI, cIAI, NP, or other infections) on CL and central volume of distribution (Vc) were fixed to those estimated from previous adult PK models. • The PK models were used to predict exposure metrics and support dosage recommendation in: ▪ Patients with NP from birth to <18 years with normal renal function or eGFR >50 mL/min/1.73m^2 for those aged ≥2 years. ▪ Patients with NP, cUTI or cIAI from 2 to <18 years with an eGFR ≤50 mL/min/1.73m^2. • The PK dataset used for modeling did not include participants with end stage renal disease (ESRD) or on intermittent hemodialysis (HD). To support dosage recommendations via PK simulations in patients 2 to <18 years old with ESRD on intermittent HD, the effect of ESRD off-HD days and the effect of HD (during a 4-hour HD) on CL and Vc were fixed to those estimated from previous PK models in adults. • PK simulations were also performed for the assessment of the probability of target attainment (PTA) in epithelial lining fluid (ELF) for NP patients and in plasma for cUTI or cIAI patients. To simulate ELF concentrations in pediatric NP patients, the transfer rate-constants of C/T from plasma into and out of ELF	• The developed PK models were considered acceptable in describing the observed concentrations of ceftolozane and tazobactam and their variability in pediatric patients (birth to <18 years) with NP, cUTI, cIAI, and other infections. The PK models were considered fit to perform PK simulations and support C/T dosage recommendations in pediatric patients from birth to <18 years with normal or impaired renal function. • Compared to the exposure (AUC) from the approved C/T dosage in adults with NP, the Applicant's originally proposed dosage resulted in lower exposure in patients with NP aged 2 to <18 years with eGFR >50 mL/min/1.73m^2 and those with severe renal impairment (15 to <30 mL/min/1.73 m^2). • Based on the review team advice to increase the C/T dosage in pediatric patient with NP (2 to <18 years) to match the adult exposure, the Applicant increased the originally proposed C/T dosage by 25% (**Table 15-10** and **Table 15-11**) with a duration of infusion of 2 hours (instead of 1 hour) in NP patients 2 years to <18 years across the following renal function groups: ▪ eGFR >50 mL/min/1.73m^2, ▪ eGFR 50 to 30 mL/min/1.73m^2, and ▪ eGFR 15 <30 mL/min/1.73m^2 (severe renal impairment). • No dose adjustment (compared to the Applicant's originally proposed dosage) was

were incorporated in the pediatric models and fixed to those estimated from previous PK models in adults with NP.	needed in patients with NP aged 2 to <18 years on intermittent HD. • No dose adjustment (compared to the Applicant's originally proposed dosage) was needed in pediatric patients with NP from birth to <2 years of age with normal renal function. • No dose adjustment (compared to the Applicant's originally proposed dosage) was needed for patients with cUTI or cIAI aged 2 to <18 years old with eGFR ≤50 mL/min/1.73m^2, as their exposure matched the exposure from the approved dosage in cUTI and cIAI patients 2 to <18 years with eGFR >50 ml/min/1.73m^2 or the exposure in adults with cUTI or cIAI on intermittent HD

15.2.3.1. Applicant's PK Analyses

The Applicant developed a pediatric PK model for ceftolozane and tazobactam in pediatric participants (birth to <18 years of age) with various infections, including cUTI, cIAI, NP, and proven or suspected gram-negative bacterial infections.

For the development of the pediatric PK model, the Applicant leveraged information established from previously developed PK models in adults with various infections (cUTI, cIAI, NP) and renal impairment (RI) to describe the covariate effects of renal function and infection type on the PK of ceftolozane and tazobactam (due to the limited data available for the pediatric population).

The data for pediatric PK modeling were collected from 4 clinical studies, including one Phase 1 study (MK-7625A-036 [P036]) conducted in participants with NP, two Phase 2 studies conducted in participants with cUTI (MK-7625A-034 [P034]) and cIAI (MK-7625A-035 [P035]) and one Phase 1 study (CXA-PEDS-13-08/MK-7625A-010 [P010]) conducted in participants with proven/suspected gram-negative bacterial infections (**Table 15-6**).

The final PK dataset used for analysis consisted of 717 and 604 quantifiable plasma concentrations for ceftolozane and tazobactam, respectively, collected from 233 participants. Concentrations below the limit of quantification (2 for ceftolozane and 113 for tazobactam) were excluded from the analysis dataset. The large proportion of BLQ concentrations for tazobactam was largely a result of the study designs, which included sample collection times >5 hours post-dose to primarily characterize the PK of ceftolozane, which has a longer half-life.

Table 15-7 summarizes the demographic characteristics of subjects included in the PK analyses, stratified by study. The PK dataset included information regarding the gestational age (GA) from

52 participants birth to <2 years of age, which enabled the evaluation of postmenstrual age (PMA) during model development to account for renal maturation in younger participants.

Table 15-6. Studies Included in the Population PK Analyses

Study	Number of Enrolled Participants	Number of Participants With Evaluable PK	Population	Dosing Regimen	PK Measurements
CXA-PEDS-13-08 or MK-7625A-010 (P010)	35	35	Pediatric participants receiving standard of care antibiotic therapy for proven or suspected gram-negative infection or for perioperative prophylaxis	C/T administered as 1-hour infusion every 8 hours	For Groups 1 to 4, plasma samples were collected at 0, 0.5 (optional), 1, 2, 4, and 6 hours after start of infusion
			Group 1: 12 to <18 years	Group 1 (n = 6): 1.5 g C/T	
			Group 2: 7 to < 12 years	Group 2 (n = 6): 27 mg/kg C/T	
			Group 3: 2 to < 7 years	Group 3 (n = 6): 27 mg/kg C/T; and 45 mg/kg C/T	
			Group 4: 3 months to < 2 years	Group 4 (n = 6): 27 mg/kg C/T; and 45 mg/kg C/T	
			Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months	Group 5 (n = 6): 30 mg/kg C/T	For Groups 5 and 6, plasma samples were collected at 1, 2, and 6 hours after start of infusion
			Group 6: birth [≤ 32 weeks gestation, 7 days postnatal] to < 3 months	Group 6 (n = 5): 30 mg/kg C/T (if eGFR > 50 mL/min/1.73 m^2); and 18 mg/kg C/T (if eGFR ≤ 50 mL/min/1.73 m^2)	
MK-7625A-034 (P034)	133	91	Pediatric participants with cUTI, including pyelonephritis	C/T administered as 1-hour infusion every 8 hours	After administration of at least 6 doses, plasma samples were collected at end of infusion, and between 3 to 4 and 6 to 7 hours (pre-next dose) after end of infusion
			Group 1: 12 to <18 years	Group 1 (n = 20): 3:1 randomization to 1.5 g C/T or 20 mg meropenem	
			Group 2: 6 to < 12 years	Group 2 (n = 32): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem	
			Group 3: 2 to < 6 years	Group 3 (n = 29): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem	
			Group 4: 3 months to < 2 years	Group 4 (n = 31): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem	
			Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months	Group 5 (n = 21): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem	

Source: Applicant's Pharmacometric Study Report (08wwfz-report), Table 1, page 98.

Study	Number of Enrolled Participants	Number of Participants With Evaluable PK	Population	Dosing Regimen	PK Measurements
MK-7625A-035 (P035)	91	68	Pediatric participants with cIAI, including pyelonephritis	C/T administered as 1-hour infusion every 8 hours	After administration of at least 6 doses, plasma samples were collected at end of infusion, and between 3 to 4 and 6 to 7 hours (pre-next dose) after end of infusion
			Group 1: 12 to <18 years	Group 1 (n = 21): 3:1 randomization to 1.5 g C/T + 10 mg/kg metronidazole or 20 mg meropenem	
			Group 2: 6 to < 12 years	Group 2 (n = 39): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole or 20 mg meropenem	
			Group 3: 2 to < 6 years	Group 3 (n = 29): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole or 20 mg meropenem	
			Group 4: 3 months to < 2 years	Group 4 (n = 1): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole or 20 mg meropenem	
			Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months	Group 5 (n = 1): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole or 20 mg meropenem	
MK7625A-036 (P036)	40	39[a]	Pediatric participants with nosocomial pneumonia Group 1: 12 to <18 years	Group 1 (n = 8): 3.0 g C/T fixed dose	Blood samples for ceftolozane and tazobactam concentration assays and plasma PK parameters were collected from all participants over one 8-hour dosing period on Day 3 (Visit 4) of the treatment period after administration of at least 6 doses of C/T. These blood samples were collected at the following times: at the end of infusion (1 hour after start of infusion of C/T, collected within 10 minutes after the end of total dose administration); between 4 and 5 hours after start of infusion; and between 7 and 8 hours after start of infusion, but prior to the start of the next dose of C/T
			Group 2: 7 to < 12 years	Group 2 (n = 7): 60 mg/kg C/T	
			Group 3: 2 to < 7 years	Group 3 (n = 8): 60 mg/kg C/T	
			Group 4: 3 months to < 2 years	Group 4 (n = 10): 60 mg/kg C/T	
			Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months	Group 5 (n = 7): 60 mg/kg C/T	

Source: Applicant's Pharmacometric Study Report (08wwfz-report), Table 1, pages 99 and 100.

Table 15-7. Summary of Demographic Characteristics, Stratified by Study

Variable	Statistic	Study P010	Study P034	Study P035	Study P036	Overall
Baseline Age (y)	Mean (SD)	5.2058 (5.9425)	5.0422 (5.2122)	8.3101 (4.3040)	5.4525 (5.7601)	6.0891 (5.3441)
	Median	2.9167	3.0000	8.0000	2.8995	5.0000
	5th, 95th	0.078, 16.692	0.089, 16.000	2.000, 15.650	0.057, 14.981	0.088, 16.000
	Min, Max	0.036, 17.500	0.063, 17.000	0.085, 17.000	0.027, 16.636	0.027, 17.500
	n	35	91	68	39	233
Baseline Body Weight (kg)	Mean (SD)	19.88 (18.30)	21.08 (17.36)	33.28 (19.13)	23.19 (24.15)	24.81 (19.94)
	Median	14.30	15.00	28.55	13.00	18.14
	5th, 95th	2.1, 56.1	4.2, 56.1	12.7, 71.6	3.2, 68.5	3.7, 63.8
	Min, Max	1.1, 60.0	2.6, 75.3	3.1, 90.0	2.1, 90.0	1.1, 90.0
	n	35	91	68	39	233
Baseline BMI (kg/m^2)	Mean (SD)	16.51 (3.60)	16.40 (3.18)	17.85 (4.63)	16.26 (4.74)	16.82 (4.02)
	Median	15.80	15.60	16.50	15.30	15.90
	5th, 95th	11.2, 22.1	12.8, 21.6	12.2, 26.8	10.7, 25.3	11.5, 25.1
	Min, Max	7.6, 25.3	9.6, 30.5	10.4, 31.3	10.4, 33.1	7.6, 33.1
	n	35	91	68	39	233
Body Surface Area (m^2)	Mean (SD)	0.70 (0.49)	0.76 (0.45)	1.08 (0.41)	0.78 (0.58)	0.85 (0.49)
	Median	0.62	0.66	1.02	0.61	0.73
	5th, 95th	0.1, 1.6	0.3, 1.6	0.6, 1.8	0.2, 1.9	0.2, 1.7
	Min, Max	0.1, 1.7	0.2, 1.8	0.2, 2.1	0.1, 2.0	0.1, 2.1
	n	35	91	68	39	233
Baseline Serum Creatinine (mg/dL)	Mean (SD)	0.35 (0.13)	0.46 (0.19)	0.50 (0.26)	0.37 (0.23)	0.44 (0.22)
	Median	0.31	0.44	0.47	0.31	0.41
	5th, 95th	0.2, 0.5	0.2, 0.8	0.2, 0.8	0.1, 0.7	0.2, 0.8
	Min, Max	0.2, 0.8	0.1, 1.0	0.1, 1.8	0.1, 1.3	0.1, 1.8
	n	35	91	68	39	233
Baseline eGFR [Original Schwartz] ($mL/min/1.73\ m^2$)	Mean (SD)	146.17 (63.80)	130.44 (64.47)	192.16 (86.13)	181.74 (111.04)	159.40 (84.41)
	Median	154.50	129.80	175.20	148.80	144.50
	5th, 95th	58.9, 237.8	57.1, 213.1	77.0, 324.1	53.8, 380.2	57.5, 309.8
	Min, Max	30.2, 305.7	42.5, 544.4	33.1, 561.0	13.2, 530.0	13.2, 561.0
	n	35	91	68	39	233
Baseline eGFR [Modified Schwartz] ($mL/min/1.73\ m^2$)	Mean (SD)	145.07 (64.71)	129.78 (51.69)	172.60 (72.93)	176.88 (104.23)	152.46 (73.45)
	Median	145.50	131.20	163.60	165.20	139.10
	5th, 95th	58.9, 214.0	62.8, 195.8	84.0, 279.1	53.8, 366.0	60.0, 285.9
	Min, Max	30.2, 366.3	55.0, 427.8	46.2, 561.0	13.2, 530.0	13.2, 561.0
	n	35	91	68	39	233
Baseline eGFR [Bedside Schwartz] ($mL/min/1.73\ m^2$)	Mean (SD)	115.01 (41.85)	100.64 (37.85)	126.05 (54.91)	136.67 (72.30)	116.25 (52.28)
	Median	109.30	100.40	117.30	127.90	105.10
	5th, 95th	54.1, 180.9	54.1, 147.0	57.5, 209.6	49.4, 245.4	53.8, 213.4
	Min, Max	27.7, 216.1	50.5, 321.2	34.7, 421.3	12.1, 398.0	12.1, 421.3
	n	35	91	68	39	233
Gestational Age (weeks)	Mean (SD)	38.09 (4.12)	39.29 (1.28)	39.65 (1.23)	39.59 (1.18)	39.27 (2.02)
	Median	40.00	40.00	40.00	40.00	40.00
	5th, 95th	27.7, 40.0	37.4, 40.3	38.0, 40.0	37.1, 40.0	37.0, 40.0
	Min, Max	26.0, 41.0	32.0, 41.0	33.0, 41.0	34.0, 40.0	26.0, 41.0
	n	35	91	68	39	233

Source: Source: Applicant's Pharmacometric Study Report (08wwfz-report), Table 8, page 107.

(Table 15-7 continued)

Variable	Statistic	Study P010	Study P034	Study P035	Study P036	Overall
Baseline Height (cm)	Mean (SD)	95.23 (42.65)	103.55 (37.43)	130.67 (26.05)	101.95 (44.82)	109.95 (39.00)
	Median	96.70	100.00	130.70	97.00	110.00
	5th, 95th	40.1, 157.2	55.2, 167.0	96.2, 174.6	51.2, 170.0	52.3, 170.0
	Min, Max	36.2, 168.5	51.0, 178.0	54.0, 180.0	39.0, 184.0	36.2, 184.0
	n	35	91	68	39	233
Protocol Dose, n (%)	12 mg/kg	2 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
	16 mg/kg	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
	18 mg/kg	10 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (4.3)
	20 mg/kg	8 (22.9)	77 (84.6)	52 (76.5)	0 (0.0)	137 (58.8)
	30 mg/kg	8 (22.9)	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.4)
	40 mg/kg	0 (0.0)	0 (0.0)	0 (0.0)	31 (79.5)	31 (13.3)
	1000 mg	6 (17.1)	14 (15.4)	16 (23.5)	0 (0.0)	36 (15.5)
	2000 mg	0 (0.0)	0 (0.0)	0 (0.0)	8 (20.5)	8 (3.4)
Sex, n (%)	Male	18 (51.4)	35 (38.5)	45 (66.2)	21 (53.8)	119 (51.1)
	Female	17 (48.6)	56 (61.5)	23 (33.8)	18 (46.2)	114 (48.9)
Race, n (%)	White	24 (68.6)	90 (98.9)	60 (88.2)	29 (74.4)	203 (87.1)
	Black or African American	7 (20.0)	0 (0.0)	5 (7.4)	2 (5.1)	14 (6.0)
	Asian	0 (0.0)	1 (1.1)	2 (2.9)	0 (0.0)	3 (1.3)
	Other	4 (11.4)	0 (0.0)	1 (1.5)	8 (20.5)	13 (5.6)
Baseline Age Group (P034/P035), n (%)	Birth (> 32 wk gestation) to < 3 m	NA	14 (15.4)	1 (1.5)	NA	15 (6.4)
	3 m to < 2 y	NA	23 (25.3)	0 (0.0)	NA	23 (9.9)
	2 to < 6 y	NA	21 (23.1)	21 (30.9)	NA	42 (18.0)
	6 to < 12 y	NA	19 (20.9)	30 (44.1)	NA	49 (21.0)
	12 to < 18 y	NA	14 (15.4)	16 (23.5)	NA	30 (12.9)
Baseline Age Group (P010/P036), n (%)	Birth (≤ 32 wk gestation) to < 3 m	5 (14.3)	NA	NA	0 (0.0)	5 (2.1)
	Birth (> 32 wk gestation) to < 3 m	6 (17.1)	NA	NA	7 (17.9)	13 (5.6)
	3 m to < 2 y	6 (17.1)	NA	NA	10 (25.6)	16 (6.9)
	2 to < 7 y	6 (17.1)	NA	NA	7 (17.9)	13 (5.6)
	7 to < 12 y	6 (17.1)	NA	NA	7 (17.9)	13 (5.6)
	12 to < 18 y	6 (17.1)	NA	NA	8 (20.5)	14 (6.0)
Infection Type, n (%)	cUTI	0 (0.0)	91 (100.0)	0 (0.0)	0 (0.0)	91 (39.1)
	cIAI	0 (0.0)	0 (0.0)	68 (100.0)	0 (0.0)	68 (29.2)
	NP	0 (0.0)	0 (0.0)	0 (0.0)	39 (100.0)	39 (16.7)
	Other Infection	35 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	35 (15.0)

Abbreviations: BMI, body mass index; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; eGFR, estimated glomerular filtration rate; Max, maximum; Min, minimum; n, number of participants; NA, not applicable; NP, nosocomial pneumonia; SD, standard deviation.

Source: Applicant's Pharmacometric Study Report (08wwfz-report), Table 8, page 108.

Final Population PK model

The PK models for ceftolozane and tazobactam consisted of 2-compartment disposition models with a constant-rate of infusion (zero-order) as an input and linear elimination from the central compartment. The PK models were parameterized in terms of clearance (CL), intercompartmental clearance (Q), central and peripheral volumes of distribution (Vc and Vp). Between-subject variability (exponential model) was estimated for CL and Vc parameters, for both the ceftolozane and tazobactam PK models. The residual unexplained variability (RUV) was described by a proportional error model, for both PK models. The parameter estimates and covariate model equations from the final PK models are listed in **Table 15-8** for ceftolozane and **Table 15-9** for tazobactam.

For both PK models, weight was included as a covariate on clearances (CL and Q) using allometric scaling with fixed exponent of 0.75, and on volumes parameters (Vc and Vp), using shared estimated exponent.

Renal maturation for CL was described using a published and accepted renal maturation function based on PMA (Rhodin MM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009 Jan;24(1):67-76).

For participants ≥2 years of age, eGFR (calculated by bedside Schwartz equation) was included as a covariate CL to describe the effect of renal function on ceftolozane and tazobactam elimination. The effect of eGFR on CL was described by a power function with fixed exponents as estimated in the previously developed adult NP models (**Table 15-8** and **Table 15-9**). The effect of renal function was only applied to participants ≥2 years of age, as the renal function is anticipated to have matured to adult levels at approximately 2 years. In contrast, in participants <2 years of age low eGFR values could be confounded and reflect renal maturation rather than renal impairment.

Infection type (cUTI, cIAI, NP, and other infections) were included as covariate on CL and Vc parameters, based on estimated effects in the adult PK models.

The goodness of fit (GOF) plots from the final PK models are shown in **Figure 15-1** and the prediction-corrected visual predictive check (pcVPC) plots are shown in **Figure 15-2**.

Table 15-8. Parameter Estimates of the Final Ceftolozane PK Model

Parameter[a]		Final Parameter Estimate			Magnitude of Variability		
		Population Mean	%RSE	Bootstrap Mean (95% CI)	Final Estimate	%RSE	Bootstrap Mean (95% CI)
CL	Clearance (L/h)	7.06	3.84	7.12 (6.68, 7.67)	32.5 %CV	17.1	30.9 (27.0, 35.9) %CV
	Exponent of (WTKG/70) for CL	0.750	FIXED	NA			
	Exponent of (EGFRB/105.1) for CL (Adult Estimate)	0.701	FIXED	NA			
	Proportional Shift in CL for cUTI (Adult Estimate)	1.18	FIXED	NA			
	Proportional Shift in CL for cIAI (Adult Estimate)	1.43	FIXED	NA			
V_c	Central Volume of Distribution (L)	5.66	34.4	7.03 (3.66,13.4)	44.7 %CV	94.6	51.6 (13.7, 90.2) %CV
	Exponent of (WTKG/70) for V_c and V_p	0.861	3.77	0.864 (0.800, 0.924)			
	Proportional Shift in V_c for cIAI (Adult Estimate)	1.272	FIXED	NA			
	Proportional Shift in V_c for NP (Adult Estimate)	1.6	FIXED	NA			
	Proportional Shift in V_c for Other Infections (Adult Estimate)	1.712	FIXED	NA			
Q	Intercompartmental Clearance (L/h)	13.5	23.8	11.95 (3.16, 18.6)	NE	NA	NA
	Exponent of (WTKG/70) for Q	0.750	FIXED	NA			
V_p	Peripheral Volume of Distribution (L)	11.5	10.0	10.27 (5.14, 13.1)	NE	NA	NA
Proportional Residual Variability		0.0867	14.1	0.0787 (0.0545, 0.103)	29.4 %CV	NA	28.1 (23.4, 32.1) %CV
Minimum Value of the Objective Function = 3371.967							

Abbreviations: cIAI, complicated intra-abdominal infection; CI, confidence interval; cUTI, complicated urinary tract infection; %CV, coefficient of variation expressed as a percent; EGFRB, estimated glomerular filtration rate; NA, not applicable; NE, not estimated; NP, nosocomial pneumonia; %RSE, relative standard error expressed as a percent; WTKG, body weight (kg).

[a] The typical value of PK parameters based on covariate effects can be calculated as follows:

if age ≥ 2, then $TVCL_i = 7.06 \times \left(\frac{WTKG_i}{70}\right)^{0.75} \times \text{RMF} \times 1.18^{cUTI} \times 1.43^{cIAI} \times \left(\frac{EGFRB_i}{105.1}\right)^{0.701}$ Else $TVCL_i = 7.06 \times \left(\frac{WTKG_i}{70}\right)^{0.75} \times \text{RMF} \times 1.18^{cUTI} \times 1.43^{cIAI}$

$$TVQ_i = 13.5 \times \left(\frac{WTKG_i}{70}\right)^{0.75}$$

$$TVVc_i = 5.66 \times \left(\frac{WTKG_i}{70}\right)^{0.861} \times 1.272^{cIAI} \times 1.6^{Pneu} \times 1.712^{other}$$

$$TVVp_i = 11.5 \times \left(\frac{WTKG_i}{70}\right)^{0.861}$$

Shrinkage estimates: 6.93% for IIV in CL and 58.2% for IIV in V_c.

$$RMF = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}} \quad ; \quad \text{PMA} = \text{age (in weeks)} + \text{gestational age (GA, weeks of pregnancy)}$$

Note: Hill coefficient was fixed to 3.4 and TM50 (renal maturation half-time) was fixed to 47.7 weeks (as in *Rhodin et al, Pediatr Nephrol. 2009 Jan;24(1):67-76*)

Source: Adapted from Applicant's Pharmacometric Study Report (08wwfz-report), Table 18, page 119.

Table 15-9. Parameter Estimates of the Final Tazobactam PK Model

Parameter[a]		Final Parameter Estimate			Magnitude of Variability		
		Population Mean	%RSE	Bootstrap Mean (95% CI)	Final Estimate	%RSE	Bootstrap Mean (95% CI)
CL	Clearance (L/h)	24.62	6.490	25.2 (22.7, 27.7)	46.0 %CV	15.60	41.5 (31.9, 49.4) %CV
	Exponent of (WTKG/70) for CL	0.75	FIXED	NA			
	Exponent of (EGFRB/105.1) for CL (Adult Estimate)	0.623	FIXED	NA			
V_c	Central Volume of Distribution (L)	6.617	27.06	7.60 (4.90, 11.6)	26.12 %CV	178.5	44.7 (5.52, 84.5) %CV
	Exponent of (WTKG/70) for V_c (and V_p)	0.8604	4.483	NA			
	Proportional Shift in V_c for cIAI (Adult Estimate)	1.49	FIXED	NA			
	Proportional Shift in V_c for NP (Adult Estimate)	2.17	FIXED	NA			
	Proportional Shift in V_c for Other Infections (Adult Estimate)	2.49	FIXED	NA			
Q	Intercompartmental Clearance (L/h)	9.556	13.95	9.43 (6.59, 12.0)	NE	NA	NA
	Exponent of (WTKG/70) for Q	0.75	FIXED	NA			
V_p	Peripheral Volume of Distribution (L)	11.03	8.545	10.97 (9.18, 13.2)	NE	NA	NA
	Proportional Shift in V_p for cIAI (Adult Estimate)	1.072	FIXED	NA			
	Proportional Shift in V_p for NP (Adult Estimate)	1.648	FIXED	NA			
	Proportional Shift in V_p for Other Infections (Adult Estimate)	0.80	FIXED	NA			
Proportional Residual Variability		0.182	10.48	0.178 (0.145, 0.218)	42.71 %CV	NA	42.20 (38.06, 46.69) %CV
Minimum Value of the Objective Function = 1062.659							

Abbreviations: cIAI, complicated intra-abdominal infection; CI, confidence interval; %CV, coefficient of variation expressed as a percent; EGFRB, estimated glomerular filtration rate; IIV, interindividual variability; NA, not applicable; NE, not estimated; NP, nosocomial pneumonia; %RSE, relative standard error expressed as a percent; WTKG, body weight (kg).

[a] The typical value of PK parameters based on covariate effects can be calculated as follows:

if age ≥ 2, then $TVCL_i = 24.62 \times \left(\frac{WTKG_i}{70}\right)^{0.75} \times \text{RMF} \times \left(\frac{EGFRB_i}{105.1}\right)^{0.623}$ Else $TVCL_i = 24.62 \times \left(\frac{WTKG_i}{70}\right)^{0.75} \times \text{RMF}$

$$TVQ_i = 9.556 \times \left(\frac{WTKG_i}{70}\right)^{0.75}$$

$$TVVc_i = 6.617 \times \left(\frac{WTKG_i}{70}\right)^{0.8604} \times 1.49^{cIAI} \times 2.17^{Pneu} \times 2.49^{other}$$

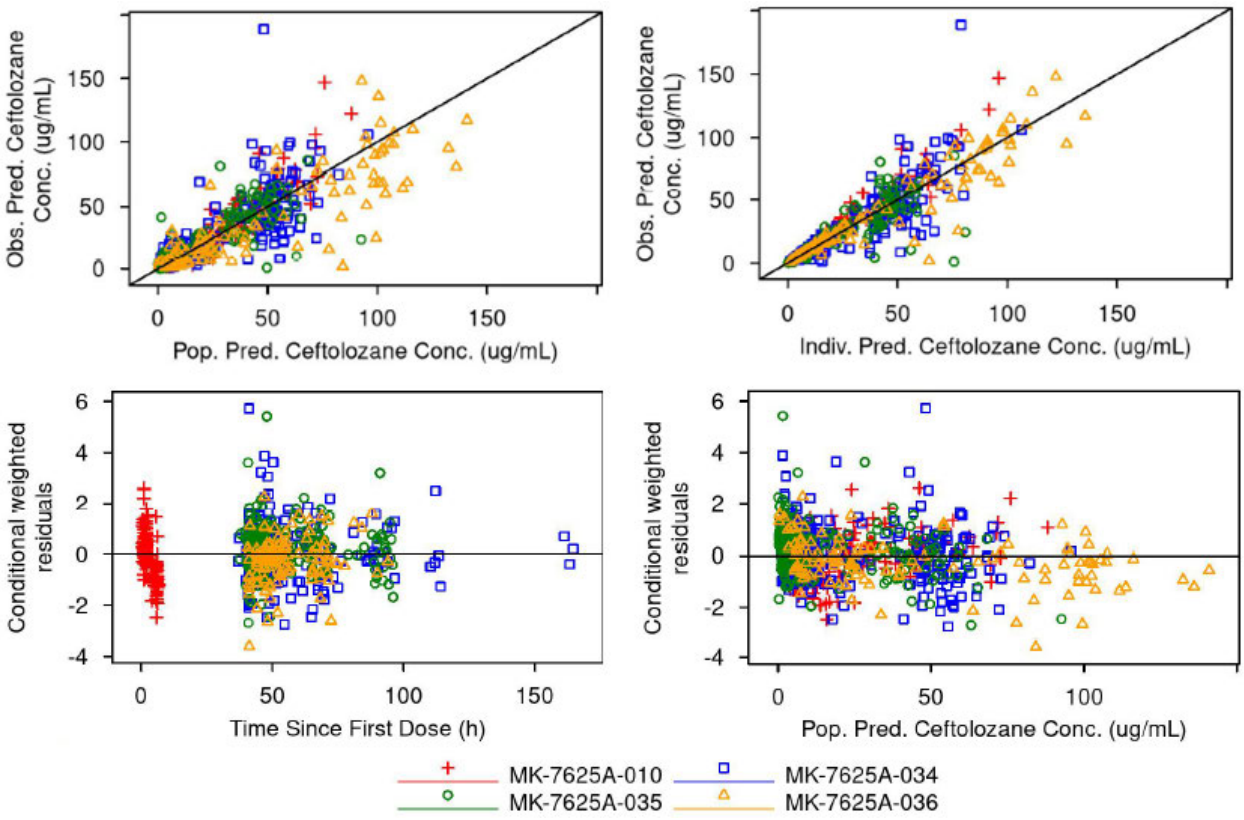
$$TVVp_i = 11.03 \times \left(\frac{WTKG_i}{70}\right)^{0.8604} \times 1.072^{cIAI} \times 1.648^{Pneu} \times 0.8^{other}$$

Shrinkage estimates: 4.78% for IIV in CL and 77.6% for IIV in V_c.

Source: Applicant's Pharmacometric Study Report (08wwfz-report), Table 19, page 120.

Figure 15-1. Goodness of Fit Plots from the Final PK model for Plasma and Urine Data

A. Ceftolozane PK data:

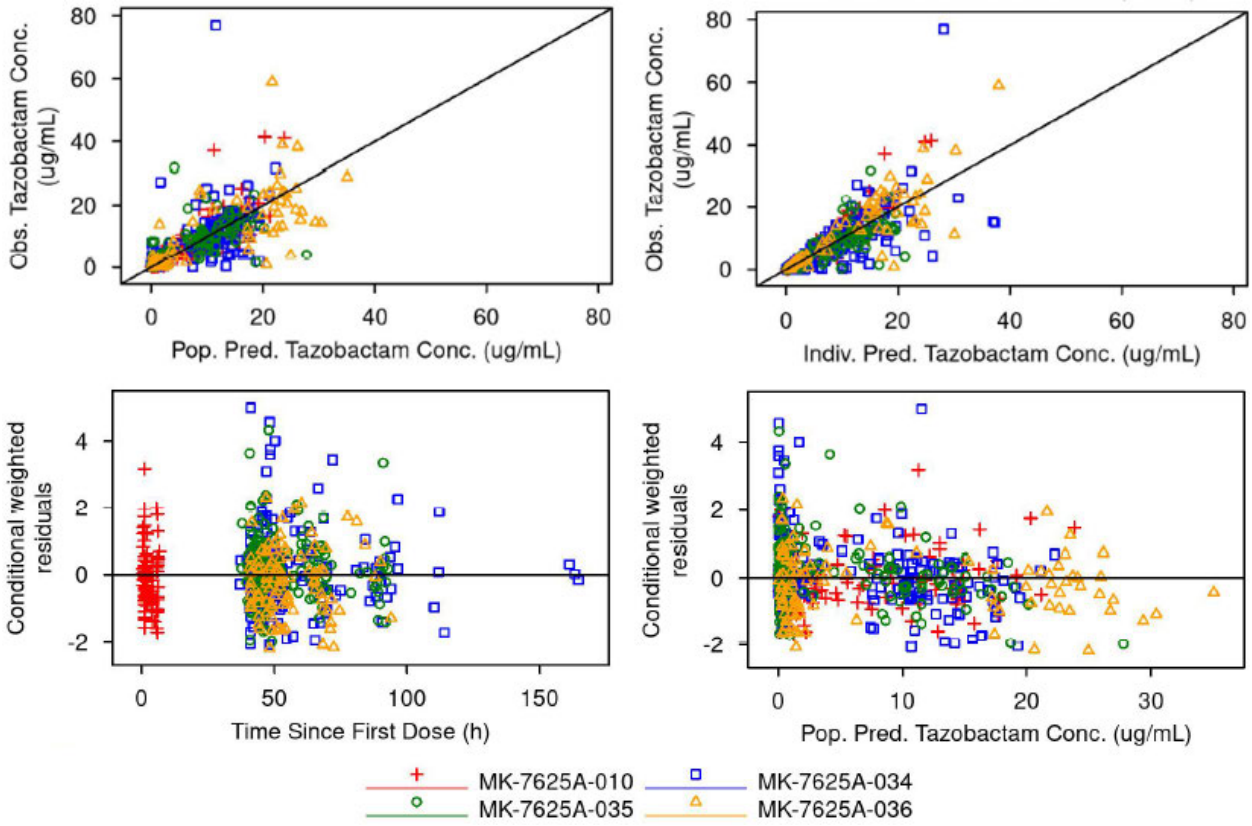


Note: Obs. Pred. Ceftolozane Conc (ug/mL) represent the observed ceftolozane concentrations in mcg/mL. The black lines represent the line of unity y = x or y = 0.

Source: Adapted from Applicant's Pharmacometric Study Report (08wwfz-report), Figure 29, pages 274 and 275.

(Figure 15-1 continued)

B. Tazobactam PK data:

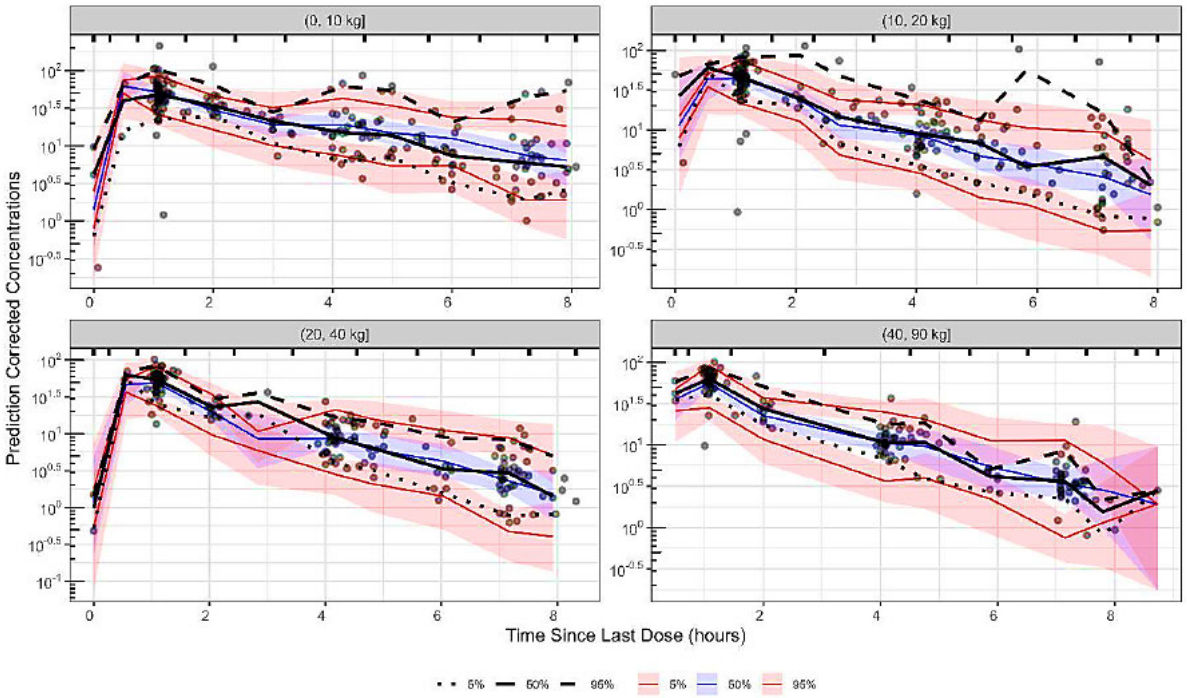


Note: The black lines represent the line of unity y = x or y = 0.

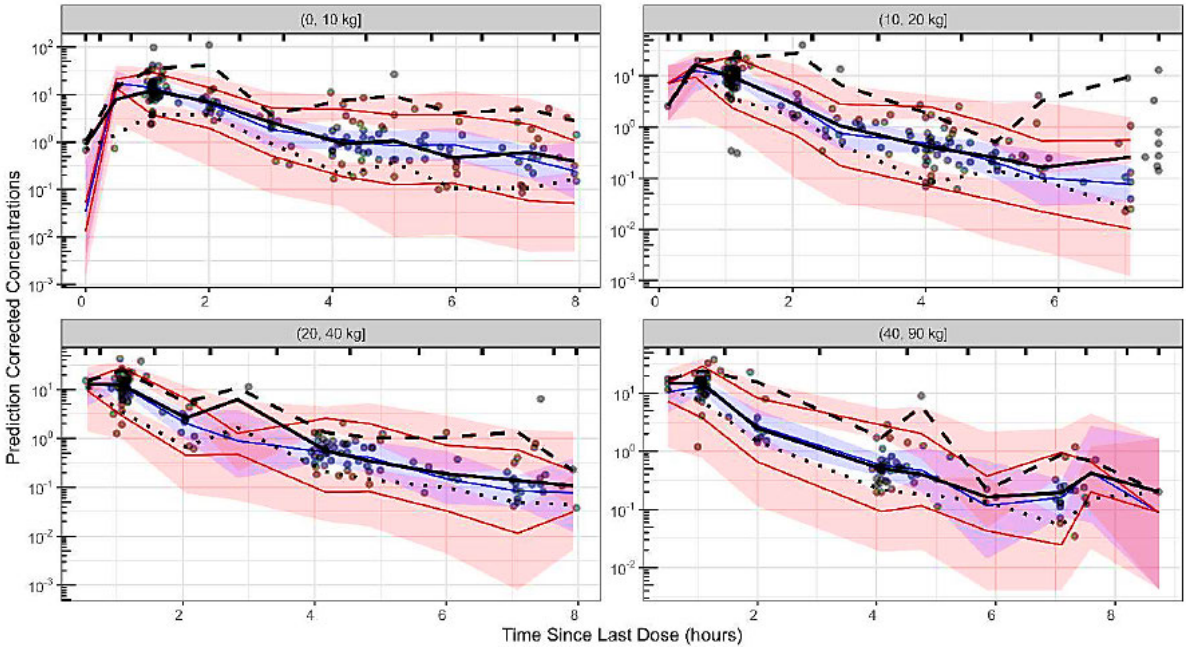
Source: Adapted from Applicant's Pharmacometric Study Report (08wwfz-report), Figure 37, pages 295 and 296.

Figure 15-2. Prediction-corrected Visual Predictive Check from Final PK Model

A. Ceftolozane:



B. Tazobactam



Notes: Circles represent individual observations. Solid lines represent the median of the observed data, and the dashed lines represent the 5th and 95th percentiles of the observed data. The dark-blue shaded areas represent the 90% CI of the median of the simulated data, and the light-red shaded areas represent the 90% CI of the 5th and 95th percentiles of the simulated data.

Source: Applicant's Response (March 12) to FDA Information request of 27 March 2026, Figures 28 and 29, pages 49 and 50.

Reviewer's Comments and Assessment of the Population PK Model:

- Overall, the Applicant's PK models are acceptable in describing the observed concentrations of ceftolozane and tazobactam and their variability in pediatric patients with NP, cUTI, cIAI, and other infections.
- The PK parameters from the PK models were estimated with an acceptable precision with the highest RSE of 34% for Vc of ceftolozane.
- The goodness of fit (GOF) plots show that the PK model fitted the observed data with no critical trends or bias in the predicted versus the observed concentrations of ceftolozane or tazobactam and in the conditional weighted residuals (CWRES) versus population predictions or time from all studies.
- The pcVPC plots stratified by study, age groups or body weight groups indicate that the Applicant's PK models are able to predict (via stochastic simulations) the observed median concentrations and their variability from all studies with no critical bias.

15.2.3.2. Application of the PK models

Ceftolozane/tazobactam (C/T) was already approved for the treatment of cUTI, cIAI and NP in adults with normal and impaired renal function (including intermittent HD) and for the treatment of cUTI and cIAI in pediatric patients from birth to <18 years old with normal renal function or eGFR >50 mL/min/1.73m^2 for those ≥2 years old (**Table 15-10**).

The Applicant used the PK models to predict C/T steady-state exposure metrics ($AUC_{0\text{-}8h}$ for a dosing interval of 8 hours, and Cmax), and perform PK simulations in a virtual pediatric population to support pediatric dosage recommendations for:

- Patients with NP from birth to <18 years of age, with normal renal function or eGFR >50 mL/min/1.73m^2 for those ≥2 years old
- Patients with NP, cUTI or cIAI from 2 to <18 years of age with an eGFR ≤50 mL/min/1.73m^2.

Table 15-10 summarizes the proposed dosage by infection type and renal function groups.

The PK dataset used for PK modeling did not include participants with end stage renal disease (ESRD) or participants on intermittent hemodialysis (HD). For PK simulations in patients ESRD on intermittent HD, the pediatric PK models were updated to account for both the effect of ESRD off-HD days (as a dichotomous covariate in addition to eGFR) and the effect of HD (during a 4-hour HD) on CL and Vc, by fixing these effects to those estimated from the previous PK models in adults.

PK simulations were also performed for the probability of target attainment (PTA) analyses in epithelial lining fluid (ELF) for NP patients and in plasma for cUTI or cIAI patients. To simulate ELF concentrations in NP patients, the transfer of C/T from plasma into and out of ELF was

incorporated into the pediatric models by fixing the transfer rate-constants to the estimated adult values.

Table 15-10. Proposed Pediatric Dosage by Infection Type and Renal Function Status

Renal Status Classification	eGFR (mL/min/1.73 m^2)	C/T Dose Ratio (mg/kg)	
		cUTI/cIAI	NP
Normal or Mild RI	> 50[a]	20/10 (up to maximum of 1000/500 mg)	40/20 (up to maximum of 2000/1000 mg)
Moderate RI	(b) (4) to 50	10/5	20/10
Severe RI	to < 30	5/2.5	10/5
ESRD (on HD)	< 15	10/5 loading dose; 2/1 maintenance dose	30/15 loading dose; 6/3 maintenance dose

Abbreviations: cIAI, complicated intra-abdominal infection; C/T, ceftolozane/tazobactam; cUTI, complicated urinary tract infection; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis; NP, nosocomial pneumonia; RI, renal impairment.

[a] General dosing recommendations apply to all pediatric patients (birth to < 18 years of age) with an eGFR according to the bedside Schwartz equation of eGFR > 50 mL/min/1.73 m^2, and pediatric patients < 2 years of age without RI (eGFR > 50 mL/min/1.73 m^2 or an eGFR at or above the limit of normal for age).

Note: The maximum C/T dose that could be administered in pediatric patients with eGFR ≤50 mL/min/1.73 m^2 was capped at the approved dose in adults with the corresponding RI category.

Source: Applicant's Pharmacometric Study Report (08wwfz-report), Table 7, page 106.

15.2.3.2.1. Simulations Supporting Dose Recommendations for NP Patients Birth to <18 Years, with Normal Renal Function or eGFR >50 mL/min/1.73 m^2 for ≥2 Years old

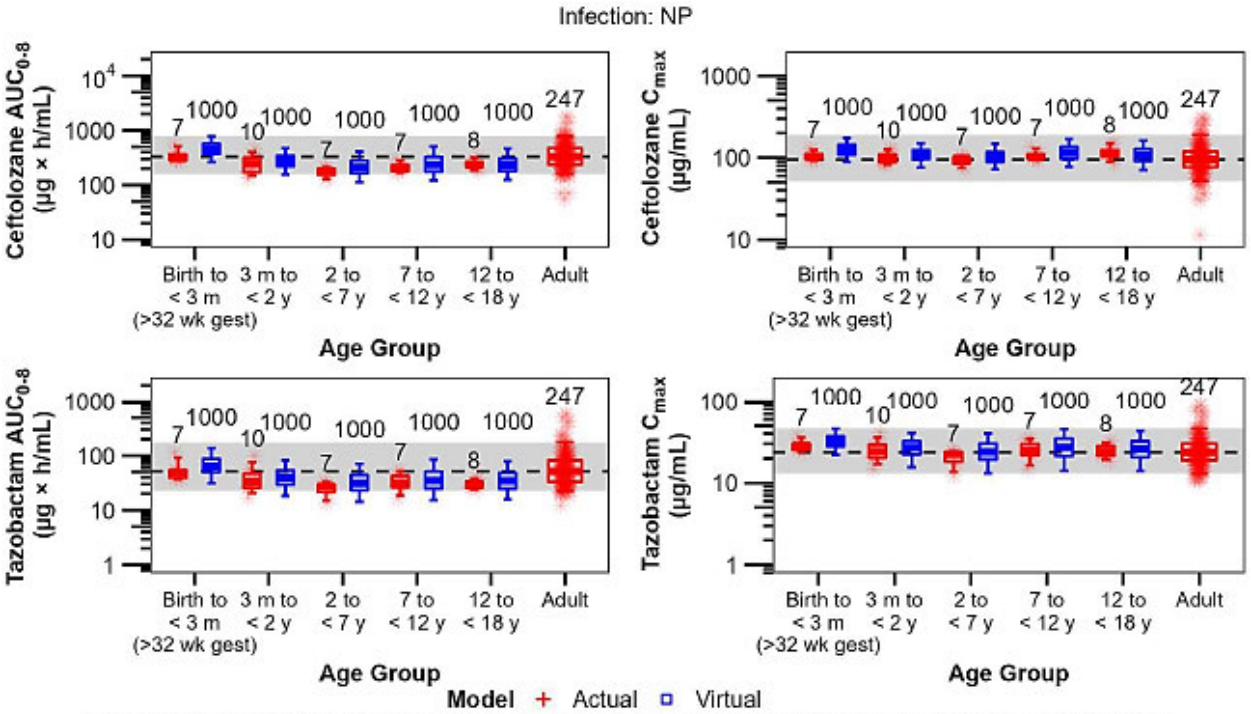
Figure 15-3 shows the comparison of the model-predicted exposure metrics for C/T between participants with NP in Study P036 receiving the protocol defined C/T dosing regimen (**Table 15-6**), the simulated exposures in virtual pediatric patients with NP receiving the proposed dosing regimen **(Table 15-10**), and adult participants with NP from Study P008 (with Creatinine Clearance >50 mL/min).

Under the proposed dosage, the boxplots of exposure metrics for C/T, stratified by age groups, show that the median and 75th percentile of AUCs in patients aged 2 years to <18 years are lower than the median AUC from the pivotal adult NP study P008. About 20% of patients aged 2 years to <18 years are predicted to have steady-state AUC below the 5th percentile of AUC in adults with NP.

In addition, the joint PTA assessment in ELF showed that >80% but less than 90% of virtual NP patients 2 to <18 years attain the joint PK/PD targets for *Pseudomonas aeruginosa* or Enterobacterales up to a MIC of 8 mcg/mL.

Based on the review team advice, the Applicant simulated C/T exposure metrics under a higher dose with a prolonged duration of infusion to match the steady-state AUCs for C/T observed in adults.

Figure 15-3. **Applicant's Proposed Dosage in 2 to <18 years Results in Lower Exposure Compared to Adults.** Model-Predicted Steady-State Exposure metrics for Ceftolozane and Tazobactam by Age Group in Participants with NP from Study P036, Virtual Pediatric Population with NP Receiving the Proposed Dosage, and Adult Participant with NP from Study P008 (with Creatinine Clearance >50 mL/min).



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. The number of patients is above each box. The dashed line and shaded region are the median and 5th to 95th percentiles of the actual adult exposure.

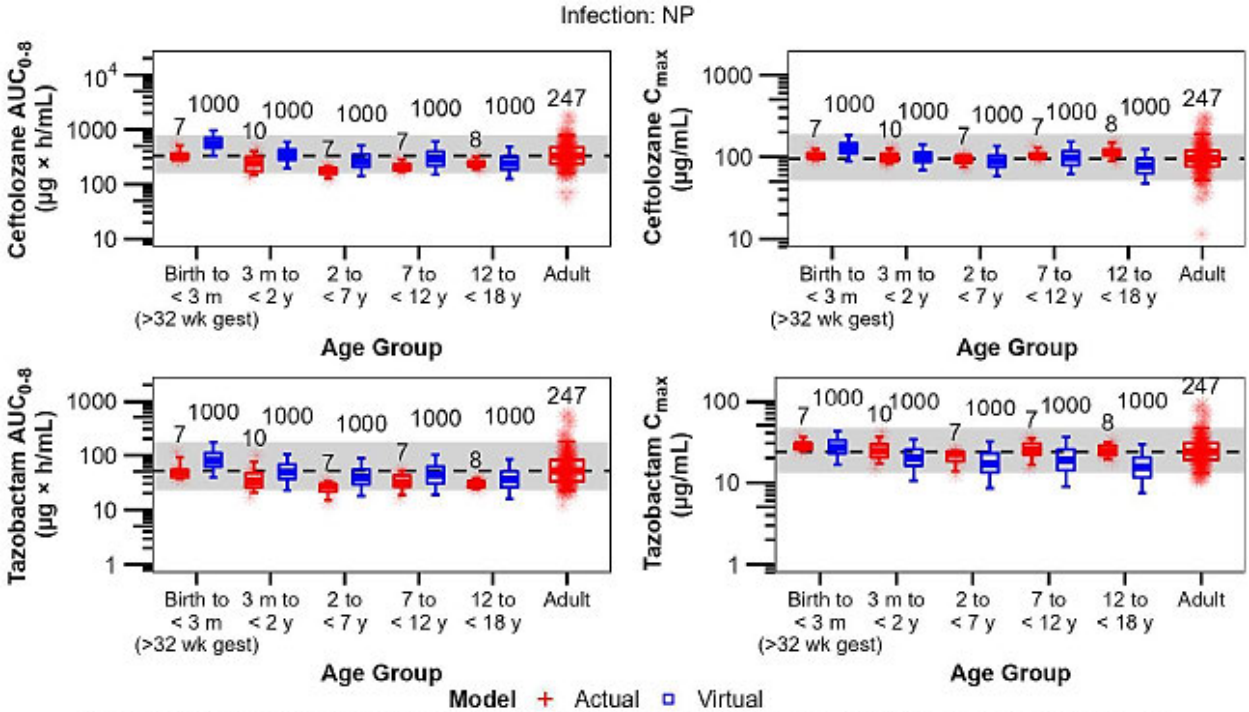
Note: the predicted exposure metrics in pediatric participant with HABP/VABP from Study P036 (red box plots) were based on the protocol defined C/T dosing regimen (i.e., 40/20 mg/kg for participants <12 years and 2/1 g C/T fixed dose for participants 12 to <18 years). The predicted exposure metrics in the virtual pediatric population was based on the proposed dosing for C/T of 40/20 mg/kg (up to a maximum of 2/1 g), infused over 1 hour. The adult exposure metrics from Study P008 are in participants with creatinine clearance >50 mL/min.
Source: Applicant's Response (April 8) to FDA Information request of 27 March 2026, Figure 1, page 6.

Figure 15-4 shows that a C/T dose of 50/25 mg/kg (up to a maximum of 2/1 g) administered over 2 hours results in predicted AUC values for C/T that are higher for pediatric HABP/VABP patients from birth to <12 years old compared to the proposed dosage. Most predicted AUC values are

within the 90% range of AUC values in adults with HABP/VABP, with approximately 10% of patients <12 years old have AUC values below the 5th percentile of AUC in adults.

In contrast, the exposures in HABP/VABP patients 12 to <18 years are comparable with the increased dosage of 50/25 mg/kg (up to a maximum of 2/1 g) compared to the proposed dosage of 40/20 mg/kg (up to a maximum of 2/1 g), given that the maximum C/T doses were capped to 2/1 g for both dosage (as approved in adults).

Figure 15-4. Applicant's Revised Dosage in 2 to <18 years Results in Improved Exposure Matching to Adults. Model-Predicted Steady-State Exposure metrics by Age Group in Virtual Pediatric Patients Population with NP Receiving Ceftolozane/Tazobactam Adjusted Dosage Compared to Participants from Study P036, and Adult Participant with NP from Study P008.



Note: The adjusted dosage is 50/25 mg/kg up to a maximum of 2/1 g, infused over 2 hours. The predicted exposure metrics in pediatric participant with NP from Study P036 (red box plots) were based on the protocol defined C/T dosing regimen (i.e., 40/20 mg/kg for participants <12 years and 2/1 g C/T fixed dose for participants 12 to <18 years). The adult exposure metrics from Study P008 are in participants with creatinine clearance >50 mL/min.
Source: Applicant's Response (April 8) to FDA Information request of 27 March 2026, Figure 5, page 19.

A dosage of 50/25 mg/kg administered over 2 hours resulted in improvement of the PTA assessment, with 96% to 100% of virtual NP patients attaining the joint PK/PD targets in ELF for

Pseudomonas aeruginosa or Enterobacterales (up to a MIC of 8 mcg/mL) across the different age groups, including in NP patients 12 to <18 years despite comparable AUC value with the proposed dosage of 40/20 mg/kg. The improvement in the joint PTA assessment in NP patients 12 to <18 years is due to the increased duration of infusion from 1 hour to 2 hours.

Reviewer's Comments:

- The reviewer team agrees with the applicant's assessments and considers that the revised C/T dosage of 50 mg/kg (up to a maximum of 2/1 g) infused over 2 hours is acceptable for patients with NP aged 2 to <18 years old (across weight groups) with eGFR >50 mL/min/1.73 m^2, to either match the exposure (AUC) in adults and/or reach a PTA >90%.
- The Applicant originally proposed dosage of 40 mg/kg infused over 1 hour is acceptable for children <2 years old (across weight groups) with normal renal function. However, in order to harmonize the duration of infusion across age groups, the Applicant proposed to increase the duration from 1 hour to 2 hours in children <2 years old with normal renal function. The reviewer team considers this adjustment acceptable, as increasing the duration of infusion without increasing the dose will result in lower Cmax but similar AUC and PTA >90%.

15.2.3.2.2. Simulations Supporting Dose Recommendations for NP Patients 2 to <18 Years with eGFR ≤50 mL/min/1.73 m^2

Figure 15-5 shows the comparison of the model-predicted exposure metrics for C/T, stratified by eGFR categories between virtual pediatric (2 to <18 years old) and adult populations with NP, receiving the protocol defined C/T dosing regimen (**Table 15-6**).

As previously discussed in NP patients aged 2 to <18 years with eGFR >50 mL/min/1.73 m^2 (**Figure 15-3** and red boxplots in **Figure 15-5**), the proposed C/T dosage in patients with severe RI (**Table 15-11** and green boxplots in **Figure 15-5**) results in lower predicted AUC values (median and 75th percentile) compared to the median predicted AUC values in adults.

Although the joint PTA assessment in ELF showed that >90% of virtual NP patients with severe RI attain the joint PK/PD targets for *Pseudomonas aeruginosa* or Enterobacterales (up to a MIC of 8 mcg/mL), the review team advised the Applicant to simulate C/T exposure metrics under a higher dose with a prolonged duration of infusion to match the predicted AUCs values for C/T in adults.

Table 15-11. Adjusted and Originally Proposed dosage by eGFR group

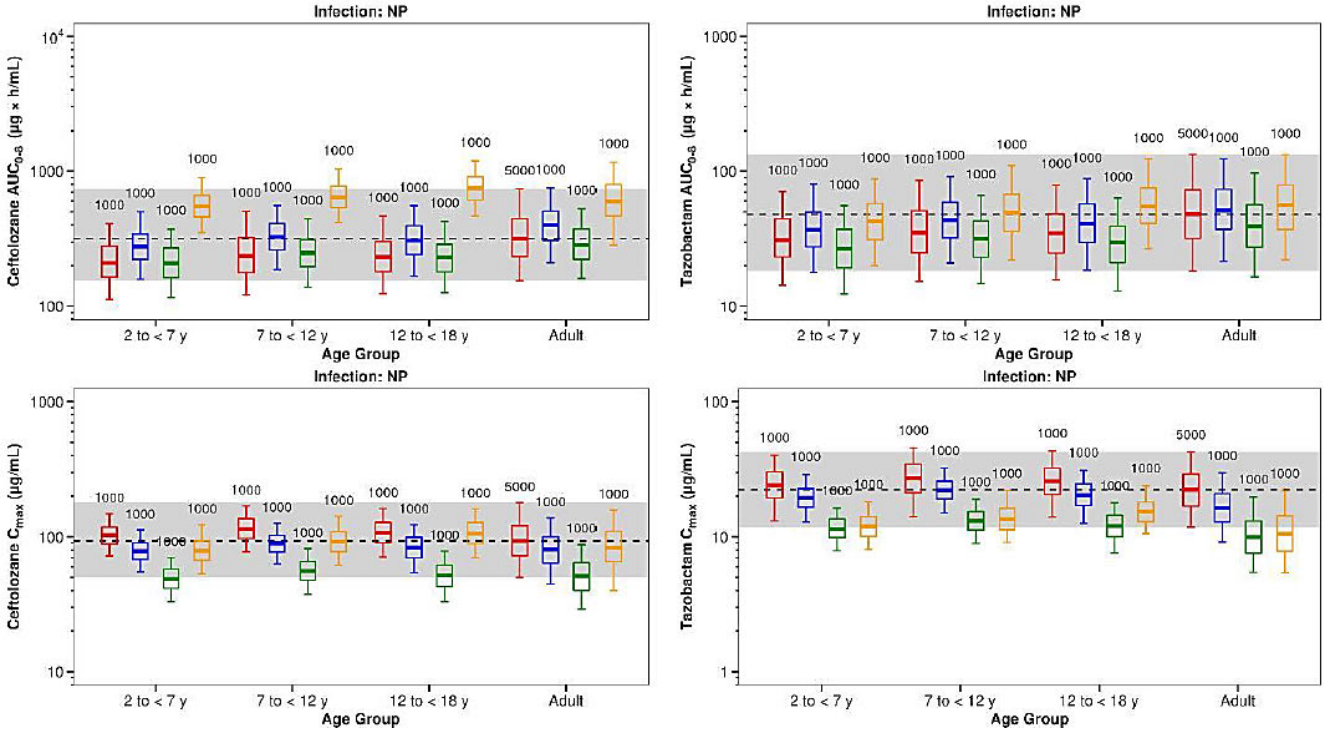
eGFR (mL/min/1.73 m^2)	Adjusted ceftolozane/tazobactam dosage capped to 2/1 g (2 hours infusion)	Originally proposed ceftolozane/tazobactam dosage capped to 2/1 g (1 hour infusion)	Approved Dosage in Adults
>50	50/25 mg/kg (up to a maximum of 2/1 g)	40/20 mg/kg (up to a maximum of 2/1 g)	2/1 g
30 to 50*	25/12.5 mg/kg	20/10 mg/kg	1/0.5 g
15 to <30 (severe RI)*	12.5/6.25 mg/kg	10/5 mg/kg	500/250 mg
ESRD on intermittent HD*	Loading: 30/15 mg/kg Maintenance: 6/3 mg/kg		Loading: 1.5/0.75 g Maintenance: 300/150 mg

Note: RI=renal impairment, ESRD=end-stage renal disease, HD=hemodialysis,
* The maximum C/T dose was capped to the approved dose in adults with the corresponding RI category.
Source: FDA reviewer

Figure 15-6 shows that the adjusted C/T dosage in NP patients with eGFR ≤50 mL/min/1.73m^2 and particularly in those with severe RI results in predicted AUC values for C/T that are higher for NP patients from 2 to <12 years old compared to the originally proposed dosage. Most predicted AUC values are within the 90% range of AUC values in adults with NP.

In NP patients 12 to <18 years with severe RI, the predicted AUC values were comparable between the adjusted and originally proposed dosage given that the maximum C/T dose in pediatric patients (≥40 kg) was capped to the approved dose in adults with the corresponding RI category.

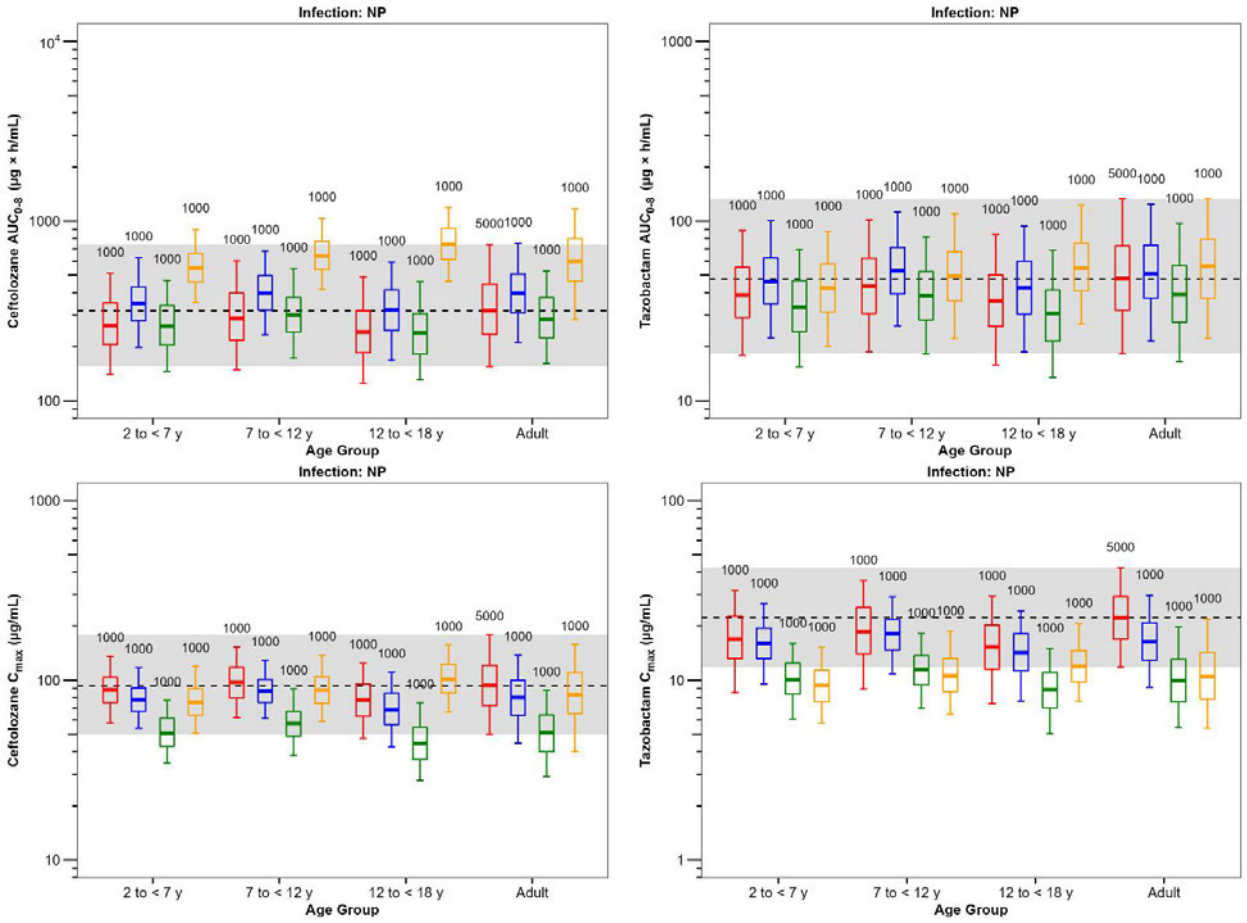
Figure 15-5. Applicant's Proposed Dosage in 2 to <18 years with eGFR >15 mL/min/1.73m^2 Results in Lower Exposure Compared to Adults. Comparison of Model-Predicted Steady-State Exposure metrics by Age Group and eGFR Category between a Pediatric Virtual Population 2 to <18 Years and Adult Virtual Patients with NP, Receiving the Proposed Dosage



Note: Red boxplots=eGFR >50 mL/min/1.73m^2 ; Blue boxplots=eGFR 30 to 50 mL/min/1.73m^2 ;
Green boxplots=severe renal impairment (eGFR 15 to <30 mL/min/1.73m^2) ;
Yellow boxplots=End Stage Renal Disease (ESRD) on intermittent hemodialysis (HD).

Note: The dashed lines and shaded areas are the median and 90% range (5th and 95th percentiles) of the exposure metrics in adults with normal renal function.
Source: Adapted from Applicant's Pharmacometric Study Report (08wwfz-report), page 16.

Figure 15-6. Applicant's Revised Dosage in 2 to <18 years with eGFR >15 mL/min/1.73m^2 Results in Improved Exposure Matching to Adults. Comparison of Model-Predicted Steady-State Exposure metrics by Age Group and eGFR Category between a Pediatric Virtual Population 2 to <18 Years and Adult Virtual Patients with NP, Receiving the Adjusted Dosage



Note: Red boxplots=eGFR >50 mL/min/1.73m^2 ; Blue boxplots=eGFR 30 to 50 mL/min/1.73m^2 ;
Green boxplots=severe renal impairment (eGFR 15 to <30 mL/min/1.73m^2) ;
Yellow boxplots=End Stage Renal Disease (ESRD) on intermittent hemodialysis (HD).

Note: The dashed lines and shaded areas are the median and 90% range (5th and 95th percentiles) of the exposure metrics in adults with normal renal function.
Source: Adapted from Applicant's Response (April 8) to FDA Information request of 27 March 2026, Figures 9-10, pages 26-27.

Reviewer's Comments:

- The reviewer team agrees with the applicant's assessments and considers that the revised C/T dosage infused over 2 hours (**Table 15-11**) is acceptable for patients with NP aged 2 to <18 years old with eGFR ≤50 mL/min/1.73 m2, to either match the exposure (AUC) in adults.

15.2.3.2.3. Simulations Supporting Dose Recommendations for cUTI and cIAI Patients 2 to <18 Years with eGFR ≤50 mL/min/1.73 m^2

C/T was already approved for the treatment of cUTI and cIAI in adults with normal and impaired renal function (including intermittent HD) and in pediatric patients from birth to <18 years old with normal renal function or eGFR >50 mL/min/1.73m^2 for those ≥2 years old **(Table 15-10**). PK simulations were performed to support dose recommendations in cUTI and cIAI patients 2 to <18 years with eGFR ≤50 ml/min/1.73m^2.

Figure 15-7 and **Figure 15-8** show the comparison of the model-predicted exposure metrics for C/T, stratified by eGFR categories between virtual pediatric (2 to <18 years old) and adult populations with cUTI and cIAI, receiving the protocol defined C/T dosing regimen.

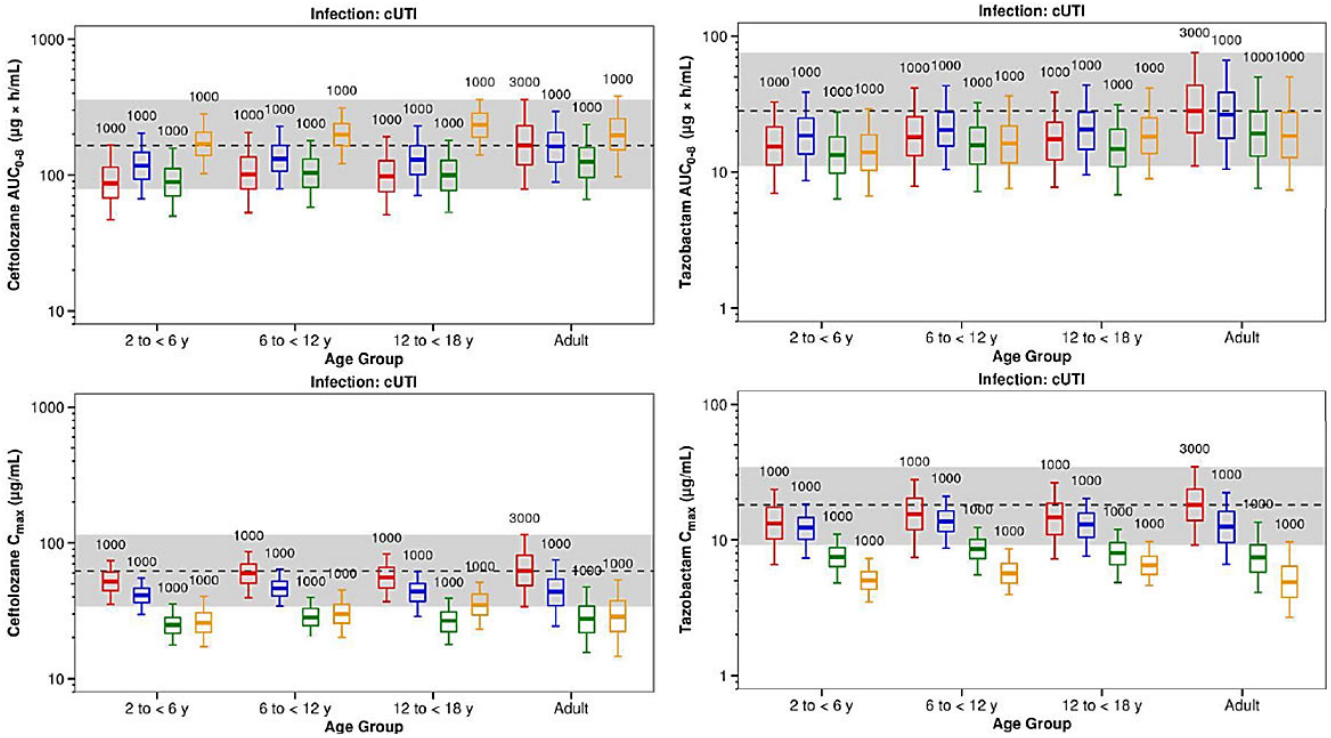
Under the proposed dosage for patients 2 to <18 years with eGFR ≤50 ml/min/1.73m^2, **Figure 15-7** (cUTI) and **Figure 15-8** (cIAI) show that the predicted AUC values for C/T in patients with eGFR 30 to 50 mL/min/1.73 m^2 (blue boxplots) and severe RI (green boxplots) are comparable to the predicted AUC values from the approved dosage in patients 2 to <18 years with eGFR >50 ml/min/1.73m^2.

The predicted AUC values in patients on intermittent HD are comparable to those estimated in adults across renal function groups for ceftolozane. For tazobactam, the predicted AUC values in patients on intermittent HD are comparable to predicted AUC values from the approved dosage in patients 2 to <18 years with eGFR >50 ml/min/1.73m^2 and adults on intermittent HD

The predicted Cmax values for C/T were lower than those predicted from the approved dosage in patients 2 to <18 years with eGFR >50 ml/min/1.73m^2, but comparable to those predicted in adults within the same eGFR category.

In addition, the joint PTA assessment in plasma showed that the proportion of virtual patients with eGFR ≤50 ml/min/1.73m^2 attaining the joint PK/PD targets for *Pseudomonas aeruginosa* or Enterobacterales (up to a MIC of 4 mcg/mL) was higher than the proportion of virtual patients with eGFR >50 ml/min/1.73m^2 receiving the approved dosage.

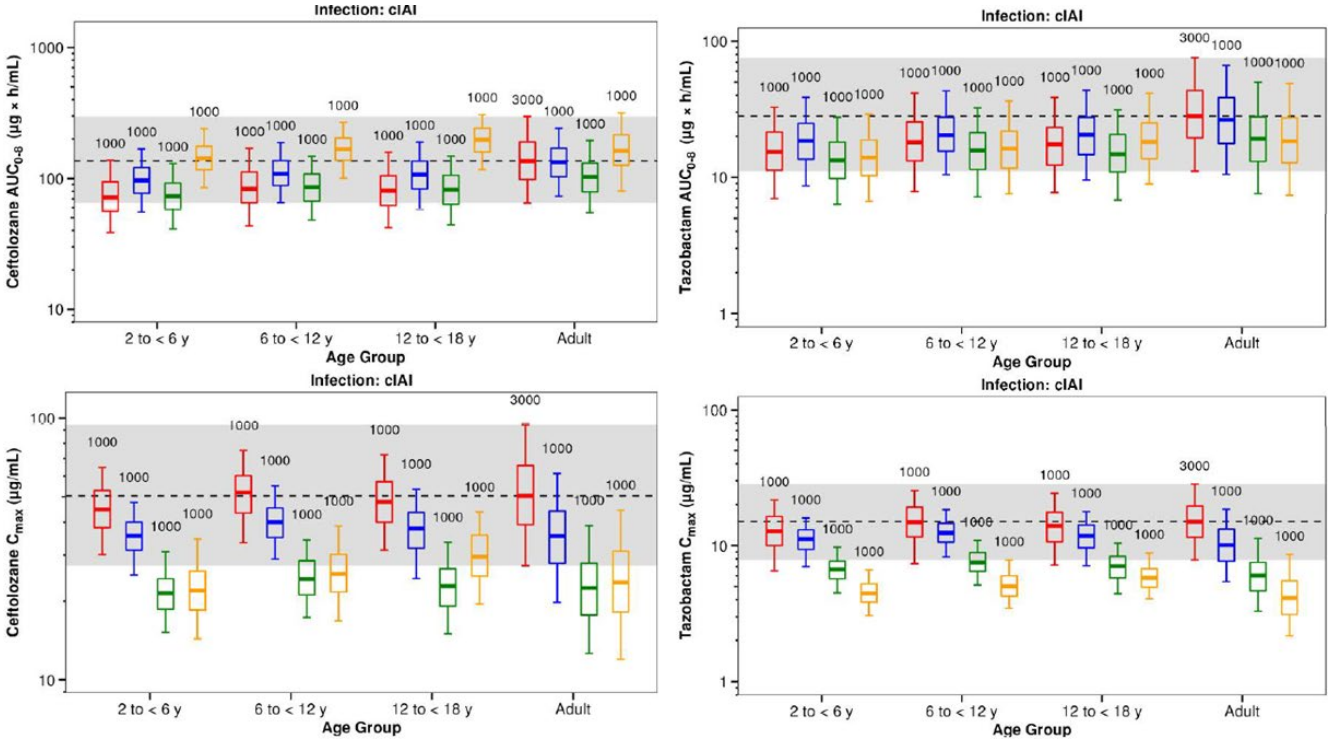
Figure 15-7. Applicant's Proposed Dosage in cUTI patients (2 to <18 years) with eGFR ≤50 mL/min/1.73 m^2 Results in Comparable Exposure to Approved Dosage in those with eGFR >50 mL/min/1.73 m^2 and Adults on HD. Comparison of Model-Predicted Steady-State Exposure metrics by Age Group and eGFR Category between a Pediatric Virtual Population 2 to <18 Years and Adult Virtual Patients with cUTI, Receiving the Proposed Dosage



Note: Red boxplots=eGFR >50 mL/min/1.73 m^2 ; Blue boxplots=eGFR 30 to 50 mL/min/1.73 m^2 ;
Green boxplots=severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2) ;
Yellow boxplots=End Stage Renal Disease (ESRD) on intermittent hemodialysis (HD).

Note: The dashed lines and shaded areas are the median and 90% range (5th and 95th percentiles) of the exposure metrics in adults with normal renal function.
Source: Adapted from Applicant's Pharmacometric Study Report (08wwfz-report), Figures 76 and 77, pages 347 and 348.

Figure 15-8. Applicant's Proposed Dosage in cIAI patients (2 to <18 years) with eGFR ≤50 mL/min/1.73 m^2 Results in Comparable Exposure to Approved Dosage in those with eGFR >50 mL/min/1.73 m^2 and Adults on HD. Comparison of Model-Predicted Steady-State Exposure metrics by Age Group and eGFR Category between a Pediatric Virtual Population 2 to <18 Years and Adult Virtual Patients with cIAI, Receiving the Proposed Dosage



Note: Red boxplots=eGFR >50 mL/min/1.73m^2; Blue boxplots=eGFR 30 to 50 mL/min/1.73m^2;
Green boxplots=severe renal impairment (eGFR 15 to <30 mL/min/1.73m^2);
Yellow boxplots=End Stage Renal Disease (ESRD) on intermittent hemodialysis (HD).

Note: The dashed lines and shaded areas are the median and 90% range (5th and 95th percentiles) of the exposure metrics in adults with normal renal function.
Source: Adapted from Applicant's Pharmacometric Study Report (08wwfz-report), Figures 78 and 79, pages 349 and 350.

Reviewer's Comments:

- The reviewer team agrees with the applicant's assessments and considers that the originally proposed C/T dosage infused over 1 hour (**Table 15-10**) is acceptable for patients with cUTI or cIAI aged 2 to <18 years old with eGFR ≤50 mL/min/1.73m^2, to either match the exposure (AUC) from the approved dosage in cUTI and cIAI patients 2 to <18 years with eGFR >50 ml/min/1.73m^2 or in adults with cUTI or cIAI on intermittent HD.

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

/s/

MUKILAN NATARAJAN
05/11/2026 05:24:08 PM