# NDA/BLA Multi-Disciplinary Review and Evaluation

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|---|---|
| **Application Type** | Efficacy Supplements |
| **Application Numbers** | NDA 206829/S-011<br>NDA 206829/S-012 |
| **Priority or Standard** | Standard |
| **Submit Dates** | **NDA 206829/S-011:** June 21, 2021<br>**NDA 206829/S-012:** July 2, 2021 |
| **Received Dates** | **NDA 206829/S-011:** June 21, 2021<br>**NDA 206829/S-012:** July 2, 2021 |
| **PDUFA Goal Date** | **NDA 206829/S-011:** April 21, 2022<br>**NDA 206829/S-012:** May 2, 2022 |
| **Division/Office** | Division of Anti-Infectives/Office of Infectious Diseases |
| **Review Completion Date** | April 19, 2022 |
| **Established/Proper Name** | ceftolozane/tazobactam |
| **(Proposed) Trade Name** | ZERBAXA |
| **Pharmacologic Class** | A combination of a cephalosporin and a β-lactamase inhibitor |
| **Applicant** | Cubist Pharmaceuticals, LLC, a subsidiary of Merck & Co., Inc. |
| **Doseage form** | Intravenous |
| **Applicant proposed Dosing Regimen** | **Complicated Intra-abdominal Infections:** 30 mg/kg (b) (4) up to a maximum dose of 1.5 g (b) (4) every 8 hrs for 5 to 14 days<br><br>**Complicated urinary tract infections including pyelonephritis:** 30 mg/kg (b) (4) up to a maximum dose of 1.5 g (b) (4) every 8 hrs for 7 to 14 days |
| **Applicant Proposed Indication(s)/Population(s)** | Addition of pediatric patients (birth to less than 18 years of age) with eGFR >50 ml/min/1.73 $m^2$ to the cIAI and cUTI indications already approved in adults |
| **Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication** | Bacterial urinary infection (disorder); Infectious disease of abdomen (disorder); |
| **Recommendation on Regulatory Action** | Approval |

| | |
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| **Recommended Indication(s)/Population(s)** (if applicable) | Treatment of complicated Intra-abdominal Infections (cIAI), used in combination with metronidazole in adult and pediatric patients<br><br>Treatment of complicated Urinary Tract Infections (cUTI) including pyelonephritis in adult and pediatric patients |
| **Recommended SNOMED CT Indication Disease Term for each Indication** (if applicable) | Infectious disease of abdomen (disorder) {128070006}<br>Urinary tract infectious disease (disorder) {68566005} |
| **Recommended Dosing Regimen** | **Complicated Intra-abdominal Infections:** 30 mg/kg up to a maximum dose of 1.5 g every 8 hrs for 5 to 14 days<br><br>**Complicated urinary tract infections including pyelonephritis:** 30 mg/kg up to a maximum dose of 1.5 g every 8 hrs for 7 to 14 days |

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OCP=Office of Clinical Pharmacology
DAI=Division of Anti-Infectives

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| **OSE/DMEPA** | Deborah Myers, RPh, MBA/ Valerie Vaughan, PharmD (TL) |

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

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# Glossary

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AR | adverse reaction |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BLA | biologics license application |
| BUN | blood urea nitrogen |
| 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 |
| $C_{max}$ | maximum concentration |
| CMC | chemistry, manufacturing, and controls |
| COA | clinical outcome assessment |
| CRO | contract research organization |
| CSR | clinical study report |
| cUTI | complicated urinary tract infections |
| C/T | ceftolozane/tazobactam |
| DAI | Division of Anti-Infectives |
| DILI | drug-induced liver toxicity |
| DNDSI | Division of New Drug Study Integrity |
| DPMH | Division of Pediatric and Maternal Health |
| DTR | difficult-to-treat resistance |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| eGFR | estimated glomerular filtration rate |
| EOIV | end of intravenous treatment visit |
| EOT | end of treatment visit |
| ESBL | Extended-Spectrum β-lactamase |
| FDA | Food and Drug Administration |
| FT | Fast Track |
| HABP | hospital-acquired bacterial pneumonia |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| ITT | intent to treat |
| IV | intravenous |
| LEVO | levofloxacin |
| MDR | multidrug-resistant |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| MERO | meropenem |
| MTZ | metronidazole |
| mITT | modified intent-to-treat |
| mMITT | microbiological modified intent-to-treat |
| NDA | new drug application |
| NP | nosocomial pneumonia |
| OCP | Office of Clinical Pharmacology |
| 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 |
| PD | pharmacodynamics |
| PeRC | Pediatric Review Committee |
| PI | prescribing information |
| PK | pharmacokinetics |
| PMR | postmarketing requirement |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PTA | probability of pharmacokinetics/pharmacodynamics target attainment |
| QIDP | Qualified Infectious Disease Product designation |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| TAZ | tazobactam |
| TEAE | treatment emergent adverse event |
| TOC | test of cure |
| TOL | ceftolozane |
| ULN | upper limit of normal |
| VABP | ventilator-associated bacterial pneumonia |

# 1 Executive Summary

## 1.1. Product Introduction

Ceftolozane/tazobactam (ZERBAXA; C/T) is a combination product containing ceftolozane, a 3'-aminopyrazolium cephalosporin, and tazobactam, a β-lactamase inhibitor, for treatment of serious infections caused by gram-negative bacteria including multi-drug resistant *P. aeruginosa* and also β-lactam-resistant Enterobacterales. Ceftolozane (TOL) exerts its bactericidal activity by inhibiting PBP3, an essential penicillin-binding protein (PBP), resulting in inhibition of cell wall synthesis and subsequent cell death. Ceftolozane also shows an affinity for all the essential PBPs (1b, 1c, and 3) in *P. aeruginosa*. Tazobactam (TAZ) is an irreversible inhibitor of β-lactamases and can bind covalently to chromosomal and plasmid-mediated bacterial β-lactamases.

ZERBAXA was initially approved on December 19, 2014, for the treatment of adults with complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI)[1]. A subsequent efficacy supplement for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) was approved on June 3, 2019[2]. The recommended dosage of ZERBAXA for injection is 1.5 gram (g) (ceftolozane 1 g and tazobactam 0.5 g) for cIAI and cUTI and 3 g (ceftolozane 2 g and tazobactam 1 g) for HABP/VABP administered every 8 hours by intravenous (IV) infusion over 1 hour in patients 18 years or older and with a creatinine clearance greater than 50 mL/min. The dose is modified for patients with impaired renal function.

The current efficacy supplements propose to add pediatric patients from birth to less than 18 years of age to the cIAI and cUTI indications. These supplements were submitted in response to the Pediatric Research Equity Act (PREA) post-marketing requirements (PMR) 2809-1 (cUTI) and 2809-2 (cIAI) for ZERBAXA. The Applicant met the dates set for study completion (December 2020) and supplemental NDA (sNDA) submission (June 2021). Efficacy supplement 011 supports the cUTI indication, and supplement 012 is for cIAI. This review analyzes the data submitted for both indications.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence to support the approval of ZERBAXA for the treatment of cIAI and cUTI in pediatric patients from birth to less than 18 years of age. Data from two double-blinded, randomized, multicenter, active-controlled studies of pediatric patients from birth to less than 18 years of age were submitted. Study 034 compared ZERBAXA to meropenem for treatment of cUTI, and Study 035 compared ZERBAXA + metronidazole

[1] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/206829Orig1s000ltr.pdf
[2] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/206829Orig1s008ltr.pdf

(MTZ) to meropenem for treatment of cIAI. The primary objective in these trials was to establish the safety and tolerability of ZERBAXA in the pediatric patient population, and secondary objectives were to evaluate ZERBAXA pharmacokinetics (PK) and efficacy. The trials were not designed for inferential testing of the efficacy of ZERBAXA to comparators in the pediatric patient population. Additionally, the Applicant submitted data from a single-dose, non-comparative, open-label study, Study P010, which evaluated the PK and safety of ZERBAXA in pediatric patients (birth to less than 18 years) receiving concurrent standard-of-care antibacterial drug therapy for treatment of proven or suspected gram-negative infection or peri-operative prophylaxis.

The safety profile of ZERBAXA in the pediatric studies was found to be similar to the safety findings observed in adults with cUTI and cIAI and no new safety signals were identified. The efficacy of ZERBAXA is extrapolated from the adult population for these indications as the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients; therefore, the cIAI and cUTI trial results are presented descriptively to support the use of ZERBAXA in the pediatric population. The extrapolation is primarily based on a ceftolozane/tazobactam exposure comparison between pediatric and adult cUTI and cIAI patients. The extrapolation is further supported by the joint ceftolozane/tazobactam probability of target attainment findings in pediatric cUTI and cIAI patients.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

ZERBAXA (ceftolozane/tazobactam; C/T) is approved for the treatment of cIAI, cUTI, and HABP/VABP in adults. These efficacy supplements propose to add pediatric patients from birth to less than 18 years of age to the cIAI and cUTI indications. The dosing regimen for both indications is age and weight-based, administered every 8 hours for 5 days (cIAI) or 7 days to 14 days (cUTI) by IV infusion over 1 hour.

Data from one single-dose, non-comparative, open-label pharmacokinetic (PK) study and two double-blinded, randomized, multicenter, active-controlled studies of pediatric patients from birth to less than 18 years of age were submitted to support the use of ZERBAXA in the proposed pediatric population. The open-label PK study enrolled 43 pediatric patients exposed to ZERBAXA with the primary objective of evaluating the PK and safety of ZERBAXA in pediatric subjects. The two double-blinded studies enrolled a total of 170 pediatric patients exposed to ZERBAXA with the primary objective of evaluating the safety and tolerability of ZERBAXA. The efficacy of ZERBAXA was extrapolated from the adult population for these indications; therefore, the cIAI and cUTI trial efficacy results were presented descriptively to support the use of ZERBAXA in the pediatric population.

The safety profile of ZERBAXA in the pediatric studies was similar to the safety findings observed in adults with cUTI and cIAI. Treatment emergent adverse events (TEAEs) occurred at a similar rate in subjects who received ZERBAXA (68%) as compared to those who received meropenem as a comparator treatment (61%). There were no deaths and no new safety signals were identified. Serious adverse events were infrequent, but did lead to discontinuation of ZERBAXA in 2 patients with cIAI. There were no concerning trends in laboratory values and no Hy's Law cases were reported. The major risks associated with ZERBAXA use include anaphylaxis and *Clostridioides difficile*-associated diarrhea (CDAD); however, these adverse reactions were not observed in the pediatric studies.

The efficacy of ZERBAXA for these indications is extrapolated from the adult population as the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients. The PK results from the clinical trials demonstrate that the ZERBAXA exposures and/or joint ceftolozane/tazobactam (C/T) probability of target attainment (PTA) findings in pediatric patients with cIAI and cUTI at the proposed doses were comparable to the exposures and/or joint C/T PTA findings in adult patients receiving the approved dose.

Overall, ZERBAXA has a favorable safety and efficacy profile for the treatment of cIAI and cUTI in pediatric patients from birth to 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 | • cIAI are serious infections that extend beyond the hollow viscus of origin into the peritoneal space and are associated with either abscess formation or peritonitis and systemic signs and symptoms of illness. The etiology of cIAI in pediatric patients depends on age group and comorbidities, and is usually treated with a combination of antibacterial drugs and surgery for source control; microbial speciation and antimicrobial susceptibility profiles of isolates taken during surgery guide treatment. Infections are typically polymicrobial and the major pathogens involved are usual residents of the gastrointestinal tract, including Enterobacterales, *Streptococci*, and anaerobes.<br>• cUTI occur in pediatric patients with underlying urological abnormalities; these abnormalities may lead to recurrent infections that may be difficult to treat, especially if the patient is exposed to multiple courses of antibacterial drugs that select for drug-resistant organisms. Infections are generally caused by gram-negative organisms, such as Enterobacterales or *Pseudomonas*. | • cIAI and cUTI are serious bacterial infections that can cause significant morbidity. Both infections may progress to sepsis and death despite appropriate management. |
| Current Treatment Options | • There are limited treatment options for cIAI and cUTI in pediatric patients caused by certain gram-negative pathogens, such as ESBL-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE) and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR). | • There is a need for new antibacterial drugs to treat infections with MDR gram-negative pathogens in pediatric patients, particularly ESBL- and carbapenemase-producing organisms and *P. aeruginosa* with DTR. |
| Benefit | • The primary objective of the trials was to establish the safety and tolerability of ZERBAXA in pediatric patients. Efficacy was a secondary endpoint, and the studies were not powered for statistical inference testing.<br>• The efficacy of ZERBAXA in the treatment of cIAI and cUTI has been established in adults. As the course of cIAI and cUTI and the effects of the | • The two pediatric studies, one each in cIAI and cUTI, provide supportive evidence of the efficacy of ZERBAXA in pediatric patients from birth to less than 18 years of age. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | drug are sufficiently similar in adult and pediatric patients, efficacy can be extrapolated from adults to pediatric patients. | • The PK results from the clinical trials demonstrate that the exposure and/or joint ceftolozane/tazobactam (C/T) probability of target attainment (PTA) findings in pediatric patients with cIAI and cUTI at the proposed doses is comparable to the exposure and/or joint C/T PTA findings in adult patients receiving the approved dose. |
| Risk and Risk Management | • Safety concerns are described in the current ZERBAXA labeling based upon experiences in the adult population with cIAI, cUTI, and HABP/VABP. The currently labeled adverse effects are consistent with those expected for an antibacterial drug of the cephalosporin class.<br>• The most serious adverse events noted in adults treated with ZERBAXA include hypersensitivity reactions and CDAD; these SAEs were not observed in the pediatric cUTI and cIAI studies.<br>• There were no deaths in the pediatric studies; 3 discontinuations due to adverse events occurred in pediatric patients treated with ZERBAXA. The causality of ZERBAXA to these adverse events resulting in discontinuation is not clear.<br>• TEAEs in the pediatric studies occurred at a similar rate in subjects who received ZERBAXA (68%) as compared to those who received meropenem as a comparator treatment (61%).<br>• There were no new safety signals in the pediatric population studied, therefore no new warnings are recommended.<br>• There are no new safety signals in post-marketing reports. | • The safety profile in pediatric patients was comparable to the previously established safety profile in adults.<br>• The most serious potential adverse events noted in the adult population, as described in the ZERBAXA prescribing information, were not observed in the pediatric population most likely due to the small size of the study population.<br>• The TEAEs associated with ZERBAXA use in the pediatric population are comparable to those reported in the adult population. These risks will be communicated in appropriate sections of the labeling, including the Adverse Reactions section. Routine postmarketing surveillance activities are recommended. There are no safety signals or potential for safety issues |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | | that require a Risk Evaluation and Mitigation Strategy (REMS). |

## 1.4. Patient Experience Data

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

| | | | | |
|---|---|---|---|---|
| ☐ | **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) | 8.1.2, 8.1.4 |
| | | ☐ | 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

Although the etiologic agents of cIAI in pediatric patients vary based on the patient's age and existing comorbidities, infections are typically caused by the gut microflora and are polymicrobial in nature. cIAI is usually treated with a combination of antibacterial drugs and surgery for source control; microbial speciation and antimicrobial susceptibility profiles of isolates from specimens taken during surgery guide treatment.

cUTI is common in pediatric patients, particularly in children with underlying urinary tract abnormalities. *Escherichia coli* is the most common pathogen implicated in UTI. Underlying anatomical abnormalities may lead to recurrent infections that are more difficult to treat, especially in patients exposed to multiple courses of antibacterial drugs that select for resistant organisms. In addition, frequent hospitalizations increase the risk for acquiring resistant organisms. Patients without exposure to antibacterial drugs or healthcare settings may also be at risk of acquiring infections with resistant organisms if they are prevalent in the community.

Both cIAI and cUTI are serious and life-threatening infections.

## 2.2. Analysis of Current Treatment Options

The following tables provide a list of therapeutic options for cUTI (Table 2-1) and cIAI (Table 2-2); comments indicate whether the drugs are approved or used off-label for pediatric patients.

**Table 2-1: Therapeutic Options for cUTI**

| Generic name | Trade name | Comments |
|---|---|---|
| **Cephalosporins: Parenteral 2nd, 3rd, and 4th generation and other cephalosporins** | | |
| Cefotetan | Cefotan | Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli.<br>Pediatric indications exist for cefoxitin (>3 months), cefuroxime (>3 months), cefotaxime (from birth), ceftazidime (from birth), ceftriaxone (>28 days), cefepime (>2 months). |
| Cefoxitin | Mefoxin | |
| Cefuroxime sodium | Zinacef | |
| Cefotaxime | Claforan | |
| Ceftazidime | Fortaz, Tazicef | |
| Ceftriaxone | Rocephin | |
| Cefepime | Maxipime | |
| Cefiderocol | Fetroja | |
| **β-lactam/β-lactamase Inhibitor Combinations** | | |
| Ceftolozane-tazobactam | Zerbaxa | Zerbaxa is used off-label in pediatric patients.<br>Avycaz is approved for pediatric patients >3 months |
| Ceftazidime-avibactam | Avycaz | |
| **Fluoroquinolones** | | |
| Levofloxacin | Levaquin | Levaquin is used off-label in pediatric patients for cUTI.<br>Ciprofloxacin is approved from age 1 for cUTI; ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions (ARs) compared to controls, including ARs related to joints and/or surrounding tissues. |
| Ciprofloxacin | Cipro | |
| **Carbapenems** | | |

| | | |
|---|---|---|
| Meropenem | Merrem | Meropenem is used off-label for cUTI in pediatric patients.<br>Imipenem is approved from birth<br>Ertapenem is approved from >3 months of age<br>Vabomere and Recarbrio are used off-label in pediatric patients. |
| Imipenem-cilastatin | Primaxin | |
| Ertapenem | Envanz | |
| Meropenem-vaborbactam | Vabomere | |
| Imipenem-cilastatin-relebactam | Recarbrio | |
| **Monobactams** | | |
| Aztreonam | Azactam | Approved from 9 months of age.<br>Although used in patients with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime. |
| **Aminoglycosides** | | |
| Gentamicin | | Gentamicin, amikacin, and tobramycin are approved from birth; however, are not considered first line therapy unless the causative organism(s) is(are) not susceptible to antibacterials having less potential toxicity.<br>Risk of nephrotoxicity and ototoxicity. |
| Amikacin | | |
| Tobramycin | | |
| Plazomicin | Zemdri | |
| **Tetracyclines** | | |
| Minocycline | Minocin | Minocycline is not recommended under age 8 years. |
| **Polymyxins** | | |
| Polymyxin B | Poly-Rx | Polymyxin B and colistimethate have pediatric indications from infancy.<br>Some gram-negative bacteria are intrinsically resistant (e.g. *Proteus* spp. *Providencia* spp. *Serratia* spp., *B. cepacia*), safety risks including nephrotoxicity and rare but serious neurotoxicity. |
| Colistimethate | Coly-mycin M | |
| **Sulfonamides** | | |
| Trimethoprim-Sulfamethoxazole | Bactrim | Contraindicated under age 2 months; IV formulation for "severe UTI" |

## Table 2-2: Therapeutic Options for cIAI

| Generic name | Trade name | Comments |
|---|---|---|
| **Cephalosporins: Parenteral 2nd, 3rd, and 4th generation** | | |
| Cefotetan | cefotan | Use of cephalosporins as empiric monotherapy has declined with emergence of multidrug resistant gram-negative bacilli.<br>Pediatric indications exist for cefoxitin (>3 months), cefuroxime (>3 months), cefotaxime (from birth), ceftazidime (from birth), ceftriaxone (>28 days), cefepime (>2 months). |
| Cefoxitin | Mefoxin | |
| Cefotaxime | Claforan | |
| Ceftazidime | Fortaz, Tazicef | |
| Ceftriaxone | Rocephin | |
| Cefepime | Maxipime | |
| **β-lactam/β-lactamase Inhibitor Combinations** | | |
| Ampicillin-sulbactam | Unasyn | Unasyn is used off-label for IAI in pediatric patients;<br>Zosyn is approved from 2 months of age.<br>Avycaz is approved for pediatric patients >3 months.<br>Zerbaxa is used off-label in pediatric patients. |
| Piperacillin-tazobactam | Zosyn | |
| Ceftolozane-tazobactam | Zerbaxa | |
| Ceftazidime-avibactam | Avycaz | |
| **Fluoroquinolones** | | |
| Ciprofloxacin | Cipro | Ciprofloxacin and moxifloxacin are used off-label for cIAI in pediatrics |
| Moxifloxacin | Avelox | |
| **Carbapenems** | | |
| Imipenem-cilastatin | Primaxin | Primaxin is approved from birth; meropenem from <2 weeks, and ertapenem from >3 months<br>Recarbrio is used off-label for cIAI in pediatrics. |
| Meropenem | Merrem | |
| Ertapenem | Envanz | |
| | | |
| Imipenem-cilastatin-relebactam | Recarbrio | |
| **Monobactams** | | |
| Aztreonam | Azactam | Approved from 9 months of age<br>Addition of an agent against gram-positive cocci is recommended.<br>Although used in patients with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime. |

| | | |
|---|---|---|
| **Aminoglycosides** | | |
| Gentamicin | | Pediatric indications exist for gentamicin (from age 1 week or less), amikacin (from birth), tobramycin (from age 1 week or less) |
| Amikacin | | |
| Tobramycin | | |
| **Tetracyclines** | | |
| Tigecycline | Tygacil | Vancomycin-resistant *Enterococcus faecium* activity, but *Pseudomonas aeruginosa* is intrinsically resistant to tigecycline<br>Both approved in adults only; given an increase in all-cause mortality associated with tigecycline, pediatric dosing recommendations are given for tigecycline in the case when no alternative options exist |
| Eravacycline | Xerava | |
| **Polymyxins** | | |
| Colistimethate | Coly-mycin M | Approved from infancy<br>Safety risks including nephrotoxicity and rare but serious neurotoxicity; Lack of supportive data to guide dosing; Some gram-negative bacteria are intrinsically resistant (e.g. *Proteus* spp., *Providencia* spp. *Serratia* spp., *B. cepacia*) |
| **Other** | | |
| Clindamycin | Cleocin | Approved from birth. Does not have gram-negative coverage. |
| Metronidazole | Flagyl | Used off-label in pediatrics. Used in combination with other agents (e.g., cephalosporins) for anaerobic coverage |

# 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 at a dose of 1.5 g (1 g ceftolozane and 0.5 g tazobactam), administered every 8 hrs by IV infusion over 1 hour. The approval of the indications included PREA PMRs for pediatric assessments. Supplement 011 [addressing PMR 2809-1] was submitted on June 21, 2021, and Supplement 012 [addressing PMR 2809-2] on July 2, 2021, to expand the cUTI and cIAI indications, respectively, to the pediatric population.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug (IND) application for ZERBAXA was submitted on July 1, 2009. Qualified Infectious Disease Product designation (QIDP) was granted on February 20, 2013, for the cUTI indication. Additionally, Fast Track designation (FT) was granted for the cUTI and cIAI indications on April 26, 2013, and February 20, 2013, respectively.

An initial pediatric study plan (iPSP) was submitted on April 25, 2013. A non-agreement advice letter was issued by FDA on July 19, 2013, with a request for revisions to the submitted iPSP. An amended iPSP was subsequently submitted on August 22, 2013, and an Agreed iPSP letter was issued on September 24, 2013.

On approval of ZERBAXA on December 19, 2014, two PMRs (PMR 2809-1 and PMR 2809-2) were issued[3].

> 2809-1: Conduct a randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cUTI. The dose for this study will be determined upon review of the data to be submitted by December 2016 from a single-dose, multicenter, non-comparative study assessing the pharmacokinetics (PK) of ceftolozane/tazobactam in pediatric patients ages 0 to <18 years that was initiated in June 2014.
>
> 2809-2: A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cIAI. The dose for this study will be determined upon review of the data to be submitted by December 2016 from a single-dose, multicenter, non-comparative study to assessing the PK pharmacokinetics (PK) of ceftolozane/tazobactam in pediatric patients ages 0 to <18 years that was initiated in June 2014.

On March 24, 2017, the Applicant submitted two pediatric study protocols to IND 104490 (SDN 271, cross-referenced to NDA 206829). Studies P034 (cUTI) and P035 (cIAI) would address PMRs 2809-1 and 2809-2, respectively. On November 28, 2018, the Applicant submitted several modifications to the protocols, including: (1) combining enrollment targets within age groups for Studies P034 and P035, (2) removing a limit for enrollment of pediatric patients with complicated appendicitis for Study P035, (3) removing the requirement that patients with cIAI undergo a surgical procedure in Study P035. The Division recommended that each indication include patients enrolled into each age group and that the enrolled population should be sufficient to provide PK information for both the cUTI and cIAI indications. This was based on the previous observation of lower ceftolozane exposure (i.e., post-hoc parameter estimates) in cIAI patients than in patients with cUTI and healthy volunteers, which is a similar trend observed with other antibacterial drugs. With these observations in the adult population, it would need to be determined whether the PK of C/T would be comparable between pediatric patients with cUTI and cIAI.

On May 6, 2019, amendments for both studies P034 and P035 were submitted including: (1) combining enrollment targets for the youngest age groups: Group 3 (2 to <6 years), Group 4 (3 months to <2 years), and Group 5 (birth to <3 months) between Studies P034 and P035, with a plan to enroll at least 4 subjects in each study for each of the age groups to provide PK information for C/T both in patients with cUTI and with cIAI with the combined enrollment targets for Group 3: ≥72 total, Group 4: ≥24 total, and Group 5: ≥24 total; (2) increasing the

[3] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/206829Orig1s000ltr.pdf

maximum allowed percentage of enrolled subjects with a diagnosis of complicated appendicitis from 60% to 90% in study P035; and (3) removing the requirement for surgical intervention planned or completed within 24 hours of enrollment for subjects with necrotizing enterocolitis in study P035.

On May 1, 2020, in the midst of the COVID-19 pandemic, the Applicant submitted amendments for both studies P034 and P035 to expedite enrollment and completion of the pediatric studies. The proposed update included removal of the requirement that at least 4 subjects be enrolled in each study for Group 4 (3 months to <2 years) and Group 5 (birth to <3 months). The Applicant submitted a justification that PK extrapolation in cIAI patients <2 years of age can be made for those with cUTI in the same age group by extrapolating the potential effect of age on PK in cIAI patients <2 years of age (Group 4 and 5) using a population PK model approach.

On June 19, 2020, the Applicant proposed to end enrollment early for both studies P034 and P035, with a combined total enrollment of 222 subjects, which was lower than the target overall minimum enrollment of 240 subjects. Also, this proposal reflected a decrease in the combined target minimum enrollment for Groups 3 (from 72 to 57 subjects) and 5 (from 24 to 21 subjects). This proposal was based on enrollment challenges related to the COVID-19 pandemic. The Division responded that the proposal to end enrollment early was acceptable.

On August 4, 2020, the Applicant submitted a request for deferral extension of PMR 2809-1 and 2809-2. On September 10, 2020, the deferral extension was granted with both studies' completion planned for December 2020 and final report submission planned for June 2021. Subsequently, Supplement 011 [PMR 2809-1] for the cUTI study was submitted on June 21, 2021, and Supplement 012 [PMR 2809-2] for the cIAI study was submitted on July 2, 2021.

# 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 inspections were necessary for this supplement.

On August 11, 2021, the clinical pharmacology reviewer requested a routine biopharmaceutical inspection of a site, (b) (4)., by the Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS). On September 13, 2021, DNDSI determined that an inspection was not warranted since DNDSI inspected the site in (b) (4), which falls within the surveillance interval. The inspection was conducted under the following submissions: NON-RESPONSIVE. The final classification for the inspection was No Action Indicated.

## 4.2. Product Quality

Zerbaxa is currently commercially available as an intravenous formulation for adults. The pediatric formulation is the same as the adult formulation.

## 4.3. Clinical Microbiology

Ceftolozane/tazobactam has activity against the pathogens described in the indication subsection of FDA approved labeling for adults, and these data are pertinent to pediatric patients as well. Supportive evidence includes the in vitro susceptibility testing information in pediatric patients that was previously submitted with the original NDA as well as new clinical, microbiological and PK information obtained from the pediatric studies P034 and P035. Additionally, the data previously provided with the original NDA demonstrated efficacy for this indication in adults and that the proposed drug product satisfied the combination rule as described in the FDA combination drug products guidance.

The Applicant has not proposed any changes to subsection 12.4 of the labeling, or to current breakpoints.

The full clinical microbiology review of this submission is provided in Appendix 15.3. An evaluation of the Applicant's proposal from the Agency's clinical microbiology perspective is below:

- We recommend approval of ceftolozane/tazobactam for the indication of cUTI and cIAI in pediatric patients from birth to 18 years of age as proposed by the Applicant
- There are no recommended changes to Microbiology subsection 12.4
- There are no recommended changes to breakpoints. Current FDA-recognized breakpoints are shown in the table below:

**Table 4-1: Antibacterial Susceptibility Test Interpretive Criteria for Ceftolozane/Tazobactam Recognized by FDA**

| | Minimum Inhibitory Concentrations (mcg/mL) | | | Disk Diffusion (zone diameter in mm) | | |
|---|---|---|---|---|---|---|
| **Pathogen** | **S** | **I** | **R** | **S** | **I** | **R** |
| **Enterobacteriaceae** | M-100 standard is recognized | | | >22 | 19-21 | <18 |
| ***Pseudomonas aeruginosa*** | M-100 standard is recognized | | | | | |
| ***Streptococcus* spp. Viridans Group** | M-100 standard is recognized | | | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Bacteroides fragilis*** | ≤8/4 | 16/4 | ≥32/4 | - | - | - |
| ***Haemophilus influenzae*** | M-100 standard is recognized | | | - | - | - |

S = Susceptible; I = Intermediate; R = Resistant

Source: FDA-recognized Susceptibility Test Interpretive Criteria website[4]

**Reviewer Comment:** *It is noted that the FDA approved disk breakpoints for Enterobacterales are different than that of CLSI which are S/I/R ≥21/18-20/≤17 mm, although the MIC breakpoints are the same. The breakpoints listed in the table were based on the dose for adults of 1.5g every 8 hours for the treatment of cUTI and cIAI.*

# 5 Nonclinical Pharmacology/Toxicology

There were no nonclinical data submitted in these supplements.

[4] https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria

# 6 Clinical Pharmacology

## 6.1. Executive Summary

The clinical pharmacology information submitted in these NDA supplements supports the approval of ZERBAXA (C/T) for the treatment of cUTI (including pyelonephritis) and cIAI in pediatric patients from birth and older with an estimated glomerular filtration rate (eGFR) > 50 mL/min/1.73 $m^2$. See Table 6-1 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

**Table 6-1. Summary of OCP Recommendations and Comments on Key Review Issues**

| Review Issue | Recommendations and Comments |
|---|---|
| Pivotal or supportive evidence of effectiveness and safety | Effectiveness:<br><br>The effectiveness of the Applicant proposed C/T dosage for pediatric cUTI and cIAI patients is principally supported based on the extrapolation of effectiveness from the approved C/T dosage for adult cUTI and cIAI patients. Specifically, the effectiveness extrapolation is based on the combined findings on following clinical pharmacology aspects:<br><br>1. TOL and TAZ exposure comparison between pediatric and adult cUTI and cIAI patients showed that following the Applicant's proposed pediatric C/T dosage:<br>• TOL exposures in pediatric patients were comparable to or lower than the adult exposures reported following the currently approved adult C/T dosage. In the pediatric age groups that exhibited lower TOL exposures than adult exposures, the joint probability of pharmacokinetic-pharmacodynamic target attainment (PTA) for C/T in these age group were comparable to the joint C/T findings in adults. Refer to #2 below for details.<br>• TAZ exposures in pediatric patients were comparable to the adult exposures reported following the currently approved adult C/T dosage, except for the pediatric age group of birth to 3 months. In this age group, median TAZ exposures were 1.5- to 1.9-fold higher compared to median estimates of adult patients (See Sections 6.2.1, 15.2.1.2, and 15.2.3).<br>2. Joint PTA assessment for C/T showed that at the Applicant's proposed pediatric C/T dosage, joint PTA estimates in pediatric cUTI and cIAI patients were above 90% for the current C/T susceptibility breakpoint of 2 and 4 µg/mL for Enterobacterales and *Pseudomonas aeruginosa*, respectively. See Sections 6.2.1 and 15.2.3 for additional details on joint PTA analysis findings. |

<table>
<tr><td></td><td>Additional evidence is from efficacy data in pediatrics that were obtained from two phase 2 pediatric safety, efficacy, and PK trials (i.e., trials P034 and P035) that evaluated the proposed pediatric C/T dosage (See Sections 8.1.5, 8.1.6, and 15.2.1.2).<br><br><u>Safety:</u><br><br>The evidence of safety was based on two phase 2 trials (P034 and P035) and one phase 1 trial (P010). See Section 8.2 for the evaluation of safety findings. Further safety evidence was based on the comparison of TOL and TAZ exposures in pediatric patients receiving the Applicant proposed C/T dosage and adult patients receiving the approved C/T dosage for the same indications. As noted above, the exposure comparison findings showed that TOL and TAZ exposures in pediatrics across the age range were comparable or lower to adult exposures except for TAZ exposures in the age group of birth to 3 months of age. In the birth to 3 months old age group, median TAZ AUC and $C_{max}$ estimates were 1.9-fold and 1.5-fold higher compared to the adults' estimates, respectively. See Section 6.2.1 for the detailed findings on the exposure comparison. See Section 8.2 for the evaluation of safety findings.</td></tr>
<tr><td>General dosing instructions</td><td>The recommended dosing regimen of C/T is shown in the table below:<br><br>
<table>
<tr><th>Age Range</th><th>Recommended Dosage Regimen for ZERBAXA (C/T)</th></tr>
<tr><td>Birth to <18 years with eGFR greater than 50 mL/min/1.73 m$^{2}$[a]</td><td>(b) (4) grams administered every 8 hours by 1 hour IV infusion.[b]</td></tr>
</table>
[a]eGFR as calculated using an age-appropriate equation for use in the pediatric population.<br>
[b]Pediatric patients weighing greater than 50 kg should not exceed a maximum dose of 1.5 g.<br><br>
The recommended treatment duration is 5-14 days for cIAI and 7-14 days for cUTI including pyelonephritis.<br><br>
Originally, the Applicant proposed (b) (4) The multi-disciplinary review team discussed the Applicant's proposal and recommended the use of an age-appropriate equation to assess a pediatric patient's renal function. See Section 11 for additional details on the labeling recommendations that were communicated to the Applicant. The Applicant agreed with this proposal.</td></tr>
</table>

| | |
|---|---|
| Dosing in patient subgroups (intrinsic and extrinsic factors) | For pediatric patients, no dose individualization is recommended based on intrinsic or extrinsic factors. Of note, there is no clinical experience or PK data in pediatric patients with an eGFR less than 50 mL/min/1.73 $m^2$ to inform dosage adjustment recommendations. Only one pediatric cIAI patient (within 12-18 years age group) was enrolled in Study P035 who had reported eGFR estimate below 50 mL/min/1.73 $m^2$ at one of the two renal function measure timepoints. See Sections 8.1.3 (Table 8-23) and 15.2.1.2 for additional details. |
| Labeling | The Applicant's proposed labeling was reviewed and the review team conveyed specific recommendations to the Applicant. See Labeling Recommendations in Section 11 for additional details. |

## 6.2. Comprehensive Clinical Pharmacology Review

### 6.2.1. Clinical Pharmacology Questions

**Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes, the clinical pharmacology program provides supportive evidence of effectiveness for the proposed pediatric C/T dosage for pediatric cUTI and cIAI patients. Specifically, the effectiveness of the Applicant proposed C/T dosage is principally supported based on the extrapolation of effectiveness from the approved C/T dosage for adult cUTI and cIAI patients. This extrapolation is supported by the combined clinical pharmacology information (summarized in the next section) and the assumptions that (1) C/T's activity against *P. aeruginosa* and Enterobacterales are similar in adult and pediatric patients, and (2) the pathophysiology and clinical manifestations of the course of the infectious disease for cUTI and cIAI are similar in adults and pediatrics. Also see Section 15.2.3 for additional details.

The proposed pediatric C/T dosage is also supported by the available efficacy findings from two phase 2 studies (i.e., P034-cUTI and P035-cIAI) in which the primary objective was to evaluate the safety and tolerability of C/T. As shown in Sections 8.1.2 and 8.1.4, clinical response was no lower than 80% in patients treated with C/T for both cUTI and cIAI. However, these studies were not statistically powered for comparative inferential efficacy analysis.

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

Yes, the proposed C/T dosing regimen of 30 mg/kg (b) (4), maximum of 1.5 g (b) (4) administered every 8 hours as a 1-hour IV infusion in patients from birth to <18 years of age with an eGFR >50 mL/min is acceptable primarily based on the findings related to exposure comparison between pediatric and adult patients. Additional supportive evidence for the proposed C/T dosing regimen is provided by the joint C/T PTA analysis findings. The review of submitted findings is summarized below and see Section 15.2.3 for detailed information.

1) Exposure Comparison Between Pediatric and Adult Patients

Utilizing population PK (PopPK) analysis, the steady-state plasma exposures for TOL and TAZ were estimated for pediatric patients enrolled in Study P034 (cUTI) and Study P035 (cIAI) in all age groups. These pediatric exposure estimates were compared to the exposures in adults with cUTI and cIAI receiving the approved C/T dose.

The median plasma AUC and Cmax values of TOL in pediatrics at the proposed C/T dosage were comparable or lower for all age groups compared to the exposures in adults (Figure 1, Figure 2, and Table 6-2). Whereas, the median plasma AUC and Cmax values of TAZ in pediatrics at the C/T proposed dosage were comparable or higher to the exposures in adults when combining cUTI and cIAI (Figure 1, Figure 2, and Table 6-3). Especially, in birth to < 3 months of age, median estimates for TAZ AUC and $C_{max}$ were higher than the other age groups including adults. One potential reason for this observation is the ontogeny of kidney membrane transporters, especially, organic-anion transporters (OAT1 and 3). Because TAZ is a substrate for OAT1/3 transporters, which are not fully developed in pediatric patients from birth to < 3 months of age[5], TAZ may exhibit diminished excretion and the resulting higher plasma TAZ concentrations.

**Table 6-2. TOL Adult and Pediatric Median Exposures (Pediatric to Adult Ratios) for cUTI and cIAI Patients**

| Patient Characteristics | Disease | Adult | Group 1 12 to < 18 y | Group 2 7 - < 12 y | Group 3 2 - < 7 y | Group 4* 3 mo - < 2 y | Group 5* Birth - < 3 mo |
|---|---|---|---|---|---|---|---|
| | (n = cUTI /cIAI) | (n = 156/161) | (n = 14/16) | (n = 15/27) | (n = 24/23) | (n = 22/-) | (n = 14/-) |
| | | Median | Median (pediatric:adult ratio) | | | | |
| $AUC_{0-8}$, µg*h/mL | cUTI | 199 | 177 (0.9) | 136 (0.7) | 124 (0.6) | 117 (0.6) | 154 (0.8) |
| $C_{max}$, µg/mL | | 68.5 | 73 (1.1) | 61 (0.9) | 54 (0.8) | 48 (0.7) | 41 (0.6) |
| $AUC_{0-8}$, µg*h/mL | cIAI | 151 | 118 (0.8) | 117 (0.8) | 98 (0.7) | - | - |
| $C_{max}$, µg/mL | | 53.6 | 50 (0.9) | 51 (1.0) | 44 (0.8) | - | - |

y = years, mo = months, *Due to enrollment issues, the Applicant was only able to enroll and collect PK from 1 subject within Groups 4 and 5 in cIAI study (P035).

*Source: Adapted from popPK reports 05qwch and 050zc7 (pgs 105-108), and 05qwch legacy dataset and program (cpkpool, exposure-ind, adult-posthoc).*

[5] Cheung KWK, van Groen BD, Burckart GJ et al. J Clin Pharmacol. 2019 Sep; 59 (Suppl 1):S56-69. doi: 10.1002/jcph.1489.

**Table 6-3. Aggregate (cUTI and cIAI) TAZ Adult and Pediatric Median Exposures (Pediatric to Adult Ratio)**

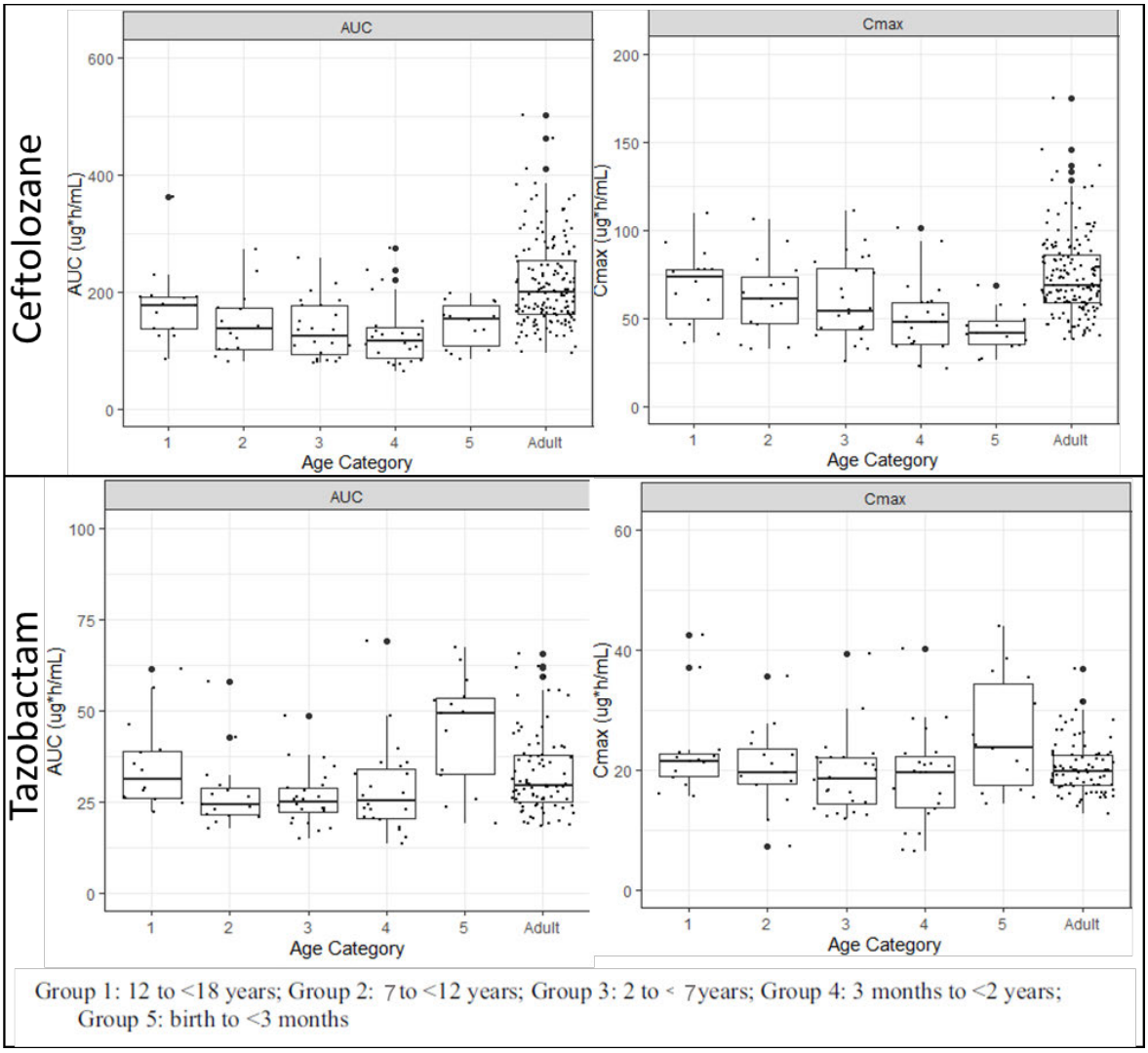
| Patient Characteristics | Disease | Adult | Group 1 12 to < 18 y | Group 2 7 - < 12 y | Group 3 2 - < 7 y | Group 4* 3 mo - < 2 y | Group 5* Birth - < 3 mo |
|---|---|---|---|---|---|---|---|
| | | n=244† | n = 30 | n = 42 | n = 47 | n = 22 | n = 14 |
| | | Median | Median (pediatric:adult ratio) | | | | |
| $AUC_{0-8}$, µg*h/mL | cUTI+cIAI | 26.7 | 28.3 (1.1) | 27.8 (1.0) | 23.8 (0.9) | 25.3 (0.9) | 49.3 (1.9) |
| $C_{max}$, µg/mL | | 16.4 | 21.3 (1.3) | 21.3 (1.3) | 17.4 (1.1) | 19.6 (1.2) | 23.7 (1.5) |

y = years, mo = months, †Total adult population consists of 83 subjects with cUTI and 161 subjects with cIAI, as one cUTI adult study (i.e., CXA-101-03) evaluated TOL only.
*Due to enrollment issues, the Applicant was only able to enroll and collect PK from 1 subject within Group 4 and 5.

Note: TAZ exposures from cUTI and cIAI studies were aggregated for each pediatric age group and adults, because infection type (cUTI and cIAI) was not identified as a significant covariate for TAZ PopPK plasma model.

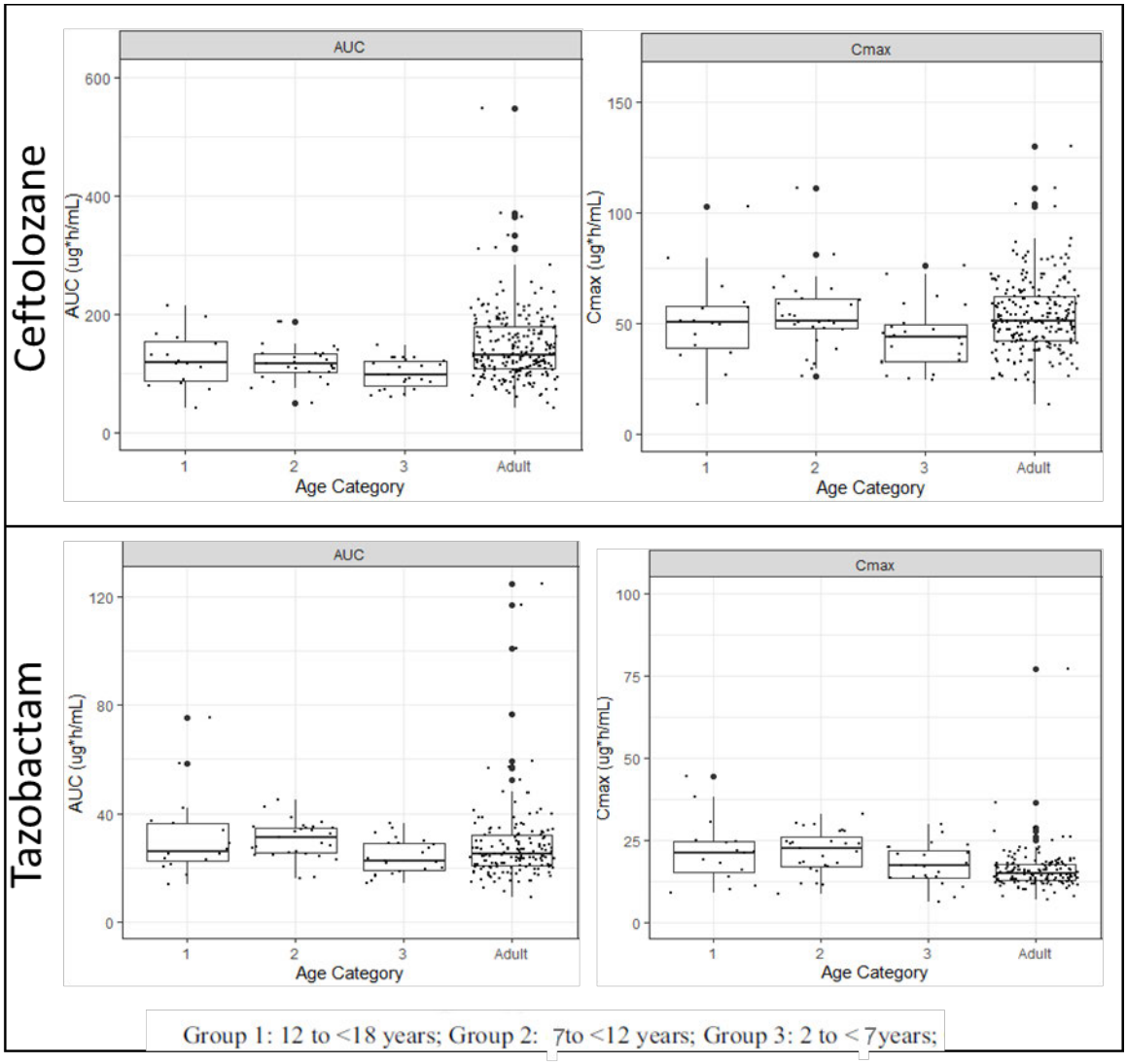
*Source: Adapted from popPK reports 05qwch and 050zc7 (pgs 105-108), and 05qwch legacy dataset and program (tpkpool, exposure-ind, adult-posthoc).*

**Figure 1: Comparison of Steady State C/T $AUC_{0-8}$ and $C_{max}$ in cUTI Participants in the Pediatric (P034) Versus Adult (Phase 2/3) Studies**




*Source: Reviewer's analysis. See the Section 15.2.3 for further details.*

**Figure 2: Comparison of Steady State C/T $AUC_{0-8}$ and $C_{max}$ in Participants with cIAI in the Pediatric (P035) Versus Adult (Phase 2/3) Studies**




*Source: Reviewer's analysis. See the Section 15.2.3 for further details.*

As noted above, the observed TOL exposures in pediatric cUTI patients were lower compared to adults in all age groups except for Group 1, i.e., 12 to <18 years of age (Figure 1, Table 6-2). The potential impact of reduced exposures in pediatric cUTI patients on TOL's effectiveness was evaluated using joint C/T PTA analysis as discussed in the next section. TOL exposures in Group 1 cUTI patients were comparable to adult cUTI patients and all pediatric age groups of cIAI patients were comparable to adult cIAI patients (Figure 1, Figure 2, and Table 6-2).

For TAZ, as noted above, the exposures in pediatric cUTI and cIAI patients were comparable to adults in all age groups except for Group 5, i.e., birth to 3 months with cUTI (Figure 1, Figure 2, and Table 6-3). Despite the numerically higher TAZ exposures in Group 5, there were minimal

drug-related TEAEs reported across all age groups in the pediatric clinical studies (see Section 8.2 for the evaluation of safety findings).

2) Joint C/T PTA Analysis

The Applicant updated the existing adult PopPK models for TOL and TAZ with pediatric PK data utilizing a Bayesian approach. The models incorporated pediatric PK data from the following studies: 1) Study P010, which consisted of intensive pediatric PK sampling in all subjects except those < 3 months of age with sparse PK sampling; 2) Study P034, which included sparse PK sampling in cUTI subjects ages birth to 18 years; and 3) Study P035, which included sparse PK sampling in cIAI subjects ages 2 to 18 years.

With the PopPK model, Monte Carlo simulations were randomly sampled from 2000 virtual cUTI and cIAI patients per age-group (referred as "Virtual dataset") to generate plasma concentration-time profiles. For the pediatric age groups ≥ 3 months of age, the virtual patient population was generated using covariance-variance relationship among age, body weight, height, and eGFR from the Applicant's internal pediatric trial database in antibacterial and antifungal programs. For the pediatric age group birth to 3 months old, the Applicant generated the virtual patient population using data for weight distributions by sex and age subgroup from the Centers for Disease Control and Prevention (CDC) data tables[6], and the eGFR were derived from data distributions reported by Schwartz and Furth[7], and Heilborn et al.[8] (referred as "Group 5 dataset"). The Applicant did not provide a rationale for using a different method to generate the Group 5 dataset, but one potential reason could be a limited number of subjects from this age group (i.e., birth to 3 months old) in the Applicant's internal pediatric trial database.

The PK-PD targets for PTA analysis were determined from a murine thigh model. Briefly, the TOL PK-PD index and target is 30% *f*T>MIC (30% of a dosing interval that the free drug concentration exceeds the MIC of the infecting organism). The TOL PK-PD target of 30% *f*T>MIC corresponds with a 1-$\log_{10}$ bacterial density reduction from a 0-hour baseline and was previously reviewed for adult cUTI and cIAI[9]. The TAZ PK-PD index and target is 20% *f*T>$C_T$ = 1 µg/mL (20% of a dosing interval that the free drug concentration remained above the threshold concentration of 1 µg/mL) which was derived from a PK-PD *in vitro* dynamic infection model and a murine thigh model. The proposed TAZ PK-PD target of 20% *f*T>$C_T$ = 1 µg/mL was previously reviewed for the adult HABP/VABP indication[10]. The protein binding for TOL and TAZ is 21% and 30%, respectively. To achieve a joint target attainment, both of the individual TOL and TAZ targets needed to be met.

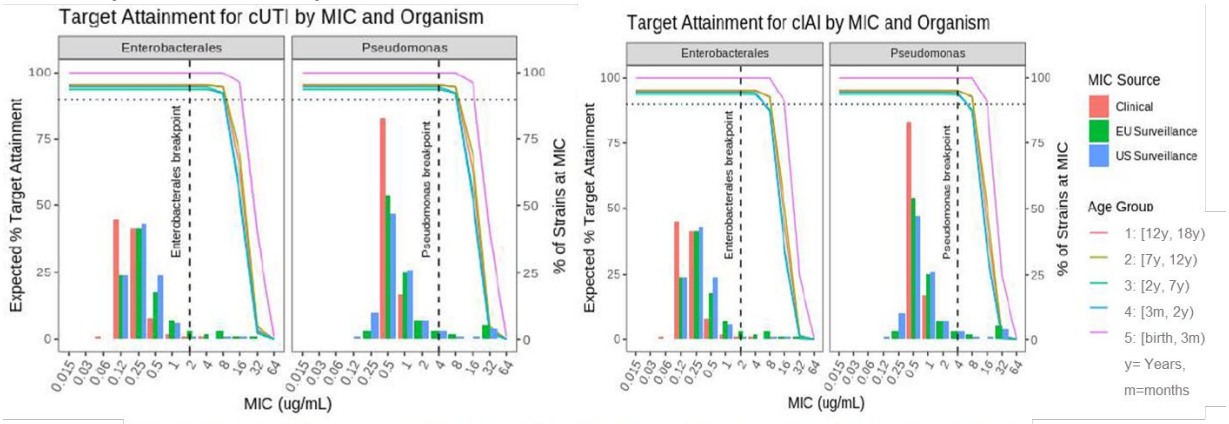
Due to enrollment issues in cIAI study (P035), the Applicant was only able to enroll and collect PK data from 1 patient within age groups 4 and 5 (i.e., birth to 2 years old). Therefore, a

[6] Fryar CD, Gu Q, Ogden CL, Flegal KM. Vital Health Stat 3. 2016 Aug;(39):1– 46.
[7] Schwartz GJ, Furth SL. Pediatr Nephrol. 2007 Nov;22(11):1839-48.
[8] Heilbron DC, Holliday MA, al-Dahwi A, Kogan BA. Pediatr Nephrol. 1991 Jan;5(1):5-11
[9] NDA206829-Suppl. 1 Clinical Pharmacology Review; DARRTS date: 10/24/2014
[10] NDA206829-Suppl. 8 Review Summary (Unireview, Clinical Pharmacology Section) DARRTS date: 05/31/2019

modeling and simulation approach was used to extrapolate the exposures from pediatric cUTI patients to support effectiveness for two cIAI age groups (i.e., birth to 3 months and >3 months to 2 years old).

The simulated exposures were used with the abovementioned TOL and TAZ PK-PD targets for determining joint C/T PTA. The Applicant's joint PTA findings showed that at the proposed C/T pediatric dosage, PTAs in pediatric cUTI and cIAI patients were above 90% for the current C/T susceptibility breakpoint of 2 and 4 µg/mL for Enterobacterales and *Pseudomonas aeruginosa*, respectively (Figure 3).

**Figure 3: Percentage of Pediatric cUTI (Left) and cIAI (Right) Patients Achieving 30% *f*T>MIC for Ceftolozane and 20% *f*T>CT in Tazobactam in Plasma at Steady State with Enterobacterales and *P. aeruginosa* with MIC Distributions Amongst Isolates from Phase 2 Studies (P034 and P035) and Surveillance Data**




The dashed vertical line represents MIC of 2 µg/mL for Enterobacterales (left panels) and MIC of 4 µg/mL for *P. aeruginosa* (right panels); the dashed horizontal line represents 90% PTA.

Abbreviations: cIAI = Complicated intra-abdominal infection urinary tract infection; *f*T>MIC = A fraction of the dosing interval that plasma concentrations remain above the minimum inhibitory concentration, *f*T>CT = A fraction of the dosing interval that free plasma concentrations remain above a threshold concentration
*Source: Adapted from the Applicant's PopPK Report 05qwch, Figure C on Page 21 (link).*

The Applicant's joint PTA findings were reviewed and the following two aspects were further evaluated by the review team by performing additional analysis summarized in the next section:

1. It was noted that the exposure estimates the Applicant used for PTA analysis for 3 months to 18 years age groups in the virtual dataset were comparable to post-hoc estimates from phase 2 studies. However, the exposures used for PTA analysis for the age group of birth to < 3 months, which used the Group 5 dataset, were 1.3 to 1.5-fold higher than the estimated post hoc exposures in the cUTI study. One potential reason for the observed differences in the age group of birth to < 3 months old could be due to differences in the methods used to generate the virtual patient population demographics of the Group 5 dataset. Specifically, as noted above, the virtual patient population for pediatric age groups ≥ 3 months of age, the virtual patient population was generated from the Applicant's internal pediatric trial database, and virtual patient

population for Group 5 dataset was generated from the CDC and other published datasets (i.e., Schwartz and Furth, and Heilborn et al.). In addition, unlike the virtual patient population for pediatric age groups ≥ 3 months of age, the Group 5 dataset is broader as it appeared to be consisting of demographic information from both infected and non-infected (e.g., healthy) pediatric subjects. Inclusion of healthy subjects may have led to higher simulated C/T exposures as healthy subjects could have lower apparent volume of drug distributions than infected subjects.

2. It was also determined that the Applicant's PTA analysis used the total TOL and TAZ concentrations instead of the free drug equivalent (i.e., based on their respective 21% and 30% protein binding) that was used in the previous C/T approvals for adult cUTI, cIAI, and HABP/VABP.

*Additional Analyses*

To evaluate the potential impact of the abovementioned review findings, the Clinical Pharmacology Review Team performed additional analyses to evaluate whether the following two observations have impact on the reported PTA findings:

i) The observed lower exposures in post-hoc estimates of birth to < 3 months old compared to the simulated estimates from the use of the Group 5 dataset

ii) The use of free TOL and TAZ concentrations instead of the total concentrations

For these analyses, the post hoc steady-state TOL concentrations were adjusted by incorporating 21% protein binding, and joint PTA was measured for the MIC of 4 µg/mL (i.e., the highest MIC susceptibility breakpoint for C/T) for all subjects in studies P034 and P035 using the TOL PK-PD target of 30% *f*T>MIC. In addition, the TOL PTAs for pediatric patients were grouped based on age and infection type. A similar approach was explored with steady-state TAZ concentrations. The TAZ concentrations were adjusted for 30% protein binding to measure a combined PTA for all subjects in studies P034 and P035 using the TAZ PK-PD target of 20% *f*T>$C_T$ = 1 µg/mL. The TAZ PTAs from each of the cUTI and cIAI subjects were combined for each pediatric age group, because infection type was not identified as a significant covariate for TAZ PopPK plasma model. The joint target attainment was achieved in >90% of the population for each age group. These findings suggested that the observed lower post-hoc exposure estimates and the use of total concentrations did not have an impact on the final conclusions drawn from the Applicant's PTA findings. See Section 15.2.3 for additional details.

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

The clinical safety data were derived from one single-dose, non-comparative, open-label study (P010) and two double-blinded, randomized, multicenter active-controlled studies in pediatric patients from birth to less than 18 years of age with cIAI (P035) and with cUTI (P034). Table 7-1 below summarizes these studies.

**Table 7-1: Listing of Clinical Trials Relevant to this NDA/BLA**

| Study number (clinicaltrials.gov identifier) | Type of study | Indication | Group /Dose/No. of patients enrolled | | | Design | Study Population |
|---|---|---|---|---|---|---|---|
| ***Studies to Support Safety*** | | | | | | | |
| Study 035 (NCT03217136) | Phase 2, randomized, active comparator-controlled, multicenter, double-blind study | cIAI | Group 1 (12 to <18 years) | TOL 1 g/and TAZ 0.5 g MTZ 10 mg/kg (maximum dose 1.5 g/day) 16 subjects | MERO 20 mg/kg (maximum 1 g/dose) 5 subjects | Randomization ratio: C/T + MTZ: MERO =3:1<br><br>Primary endpoints: safety, and tolerability of C/T plus MTZ compared with that of MERO<br><br>Sample size: C/T + MTZ: 71 randomized/ 70 treated/ 65 completed<br><br>MERO: 23 randomized/ 21 treated/ 20 completed<br><br>Treatment duration: 5-14 days<br><br>50 sites (12 countries) | Gender and median age by treatment group in the all participants as treated (APaT) population:<br><br>Overall C/T + MTZ: Gender : 67.1% M / 32.9% F Median age (range): 8.206 years (0.085 [31 days] to 17.559)<br><br>Overall MERO Gender: 28.6% M / 71.4% F Median age (range): 8.512 years (3.403 to 13.559) |
| | | | Group 2 (6 to <12 years) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum TOL 1 g and TAZ 0.5 g/dose) MTZ 10 mg/kg (maximum dose 1.5 g/day) 30 subjects | MERO 20 mg/kg (maximum 1 g/dose) 9 subjects | | |
| | | | Group 3 (2 to <6 years) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum TOL 1 g and TAZ 0.5 g/dose) MTZ 10 mg/kg (maximum dose 1.5 g/day) 22 subjects | MERO 20 mg/kg (maximum 1 g/dose) 7 subjects | | |
| | | | Group 4 (3 months to < 2 years) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum TOL 1 g and TAZ 0.5 g/dose) MTZ 10 mg/kg (maximum dose 1.5 g/day) 1 subject | MERO 20 mg/kg (maximum 1 g/dose) 0 subjects | | |
| | | | Group 5 (Birth to <3 months ) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose)<br><br>Participants >28 days of age: MTZ 10 mg/kg q 8 hours (maximum dose 1.5 g/day) | MERO 20 mg/kg (maximum 1 g/dose) 0 subjects | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | For participants ≤28 days of age, the suggested dosing regimen is listed below; however, other site-specific standard of care MTZ dosing was permitted at the investigator's discretion.<br>Participants ≤28 days of age and ≤2 kg:<br>MTZ 15 mg/kg loading dose, then 7.5 mg/kg/dose q 12 hours<br>Participants ≤28 days of age and >2 kg:<br>MTZ 15 mg/kg loading dose, 10 mg/kg dose q 8 hours<br>1 subject | | | |
| Study 034 (NCT03230838) | Phase 2, randomized, active comparator-controlled, multicenter, double-blind study | cUTI | Group 1 (12 to <18 years) | TOL 1 g/and TAZ 0.5 g<br>15 subjects | MERO 20 mg/kg (maximum 1 g/dose)<br>5 subjects | Randomization ratio C/T: MERO=3:1<br><br>Primary endpoints: safety, and tolerability of C/T compared with that of MERO<br><br>Sample size:<br>C/T: 101 randomized/ 100 treated/ 69 completed<br><br>MERO: 33 randomized/ 33 treated/ 24 completed | Gender and median age by treatment group in the APaT population:<br>Overall C/T Gender:<br>35.0% M / 65.0% F<br>Median age (range): 3.884 years (0.063 [23 days] to 17.408)<br><br>Overall MERO Gender:<br>39.4% M / 60.6% F |
| | | | Group 2 (6 to <12 years) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum TOL 1 g and TAZ 0.5 g/dose)<br>24 subjects | MERO 20 mg/kg (maximum 1 g/dose)<br>8 subjects | | |
| | | | Group 3 (2 to <6 years) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum TOL 1 g and TAZ 0.5 g/dose)<br>22 subjects | MERO 20 mg/kg (maximum 1 g/dose)<br>7 subjects | | |
| | | | Group 4 (3 months to < 2 years) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum TOL 1 g and TAZ 0.5 g/dose)<br>24 subjects | MERO 20 mg/kg (maximum 1 g/dose)<br>7 subjects | | |
| | | | Group 5 (Birth to <3 months ) | TOL 20 mg/kg and TAZ 10 mg/kg (maximum TOL 1 g and TAZ 0.5 g/dose)<br>15 subjects | MERO 20 mg/kg (maximum 1 g/dose)<br>6 subjects | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Treatment duration: 7-14 days<br><br>52 sites (10 countries) | Median age (range): 3.080 years (0.027 [10 days] to 17.800) |
| ***Clinical pharmacological studies pertinent to the review of efficacy or safety*** | | | | | | | |
| Study 010 (NCT02266706) | Phase 1, single-dose, non-comparative, open-label study | Treatment of serious gram-negative bacterial infections. | Group 1 (N=6) ≥12 to <18 years | Single IV dose, 1.5 g fixed dose of C/T (comprising 1000 mg TOL and 500 mg TAZ)<br>6 Subjects | | The primary endpoints: area under the plasma concentration-time curve (AUC) and maximum concentration ($C_{max}$) for C/T, and the TAZ metabolite (M1) as data allowed.<br><br>Sample size in completed study: 37 | Nineteen subjects (51.4%) were male and 18 (48.6%) were female, and the majority of subjects were white (67.6%)<br><br>Median age (range): 1.250 years (0.0356 [13 days] to 17.5) |
| | | | Group 2 (N=6) ≥7 to <12 years | Single IV dose, 18 mg/kg TOL and 9 mg/kg TAZ<br>6 Subjects | | | |
| | | | Group 3 (N=6) ≥2 to <7 years | Single IV dose, 18 mg/kg TOL and 9 mg/kg TAZ<br>3 Subjects | | | |
| | | | | Single IV dose, 30 mg/kg TOL and 15 mg/kg TAZ<br>3 Subjects | | | |
| | | | Group 4 (N=6) ≥3 months to <2 years | Single IV dose, 18 mg/kg TOL and 9 mg/kg TAZ<br>1 Subject | | | |
| | | | | Single IV dose, 30 mg/kg TOL and 15 mg/kg TAZ<br>5 Subjects | | | |
| | | | Group 5 (N=7) Birth (>32 weeks gestation, 7 days postnatal) to <3 months | Single IV dose, 20 mg/kg TOL and 10 mg/kg TAZ<br>7 Subjects | | | |
| | | | Group 6 (N=6) Birth (≤32 weeks | Single IV dose, 12 mg/kg TOL and 6 mg/kg TAZ<br>2 Subjects | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | gestation, 7 days postnatal) to <3 months | Single IV dose, 20 mg/kg TOL and 10 mg/kg TAZ<br>4 Subjects | | |

MERO = meropenem; MTZ = metronidazole;
Source: Reviewer generated based on 2.7.4 Summary of Clinical Safety, Clinical Study Report P010MK7625A, and review of original NDA

## 7.2. Review Strategy

The review of the data to support the cIAI and cUTI indications will be described separately. For the indications of cIAI and cUTI, efficacy in pediatrics is traditionally extrapolated from adults. Therefore, the pediatric studies were designed with relatively small sample sizes and included primary objectives of evaluating safety and tolerability. Efficacy results were assessed descriptively.

Data sources reviewed included patient-level datasets, study reports, protocols, statistical analysis plans, 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\0388\m5\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. The protocols and statistical analysis plans were sufficiently precise and comprehensive, and the Applicant's reported analyses were consistent with planned analyses.

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. Study P034

**Trial Design**

Study MK-7625A-034 (P034) was a phase 2, randomized, active comparator-controlled, multicenter, double-blind study evaluating the safety and efficacy of ceftolozane/tazobactam (C/T) versus meropenem (MERO) in pediatric participants from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cUTI, including pyelonephritis. Eligible participants were randomized in a 3:1 ratio to receive either IV C/T or IV MERO, respectively, with stratification by age groups as shown in Table 8-1.

**Table 8-1 Dosing Regimen by Age Group, Study P034**

| IV Drug | Dose/Potency | Dose Frequency[a,b] |
|---|---|---|
| **Group 1 (12 to <18 years)** | | |
| C/T | Ceftolozane 1 g and tazobactam 0.5 g | q8h |
| MERO | MERO 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 2 (6 to <12 years)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MERO | MERO 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 3 (2 to <6 years)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MERO | MERO 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 4 (3 months to <2 years)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MERO | MERO 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 5 (Birth[c] to <3 months)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MERO | MERO 20 mg/kg (maximum 1 g/dose)[d] | q8h |

**Source: Synopsis of CSR**

a- Each dose of C/T or MERO was administered as a 60-minute (± 10 minutes) infusion. C/T or MERO were to be

dosed every 8 hours (± 1 hour) after the previous infusion. The second IV dose had a ± 4-hour window for dosing to facilitate adjustment of the dosing schedule (q8h) to be performed throughout the dosing period.

b- After receiving at least 9 doses of double-blind IV study treatment, participants could be switched to open-label, standard of care, oral step-down therapy at the investigator's discretion. The total duration of study treatment (IV only or IV + oral) was a minimum of 7 days and a maximum of 14 days.

c- Birth was defined as >32 weeks gestational age and ≥7 days postnatal.

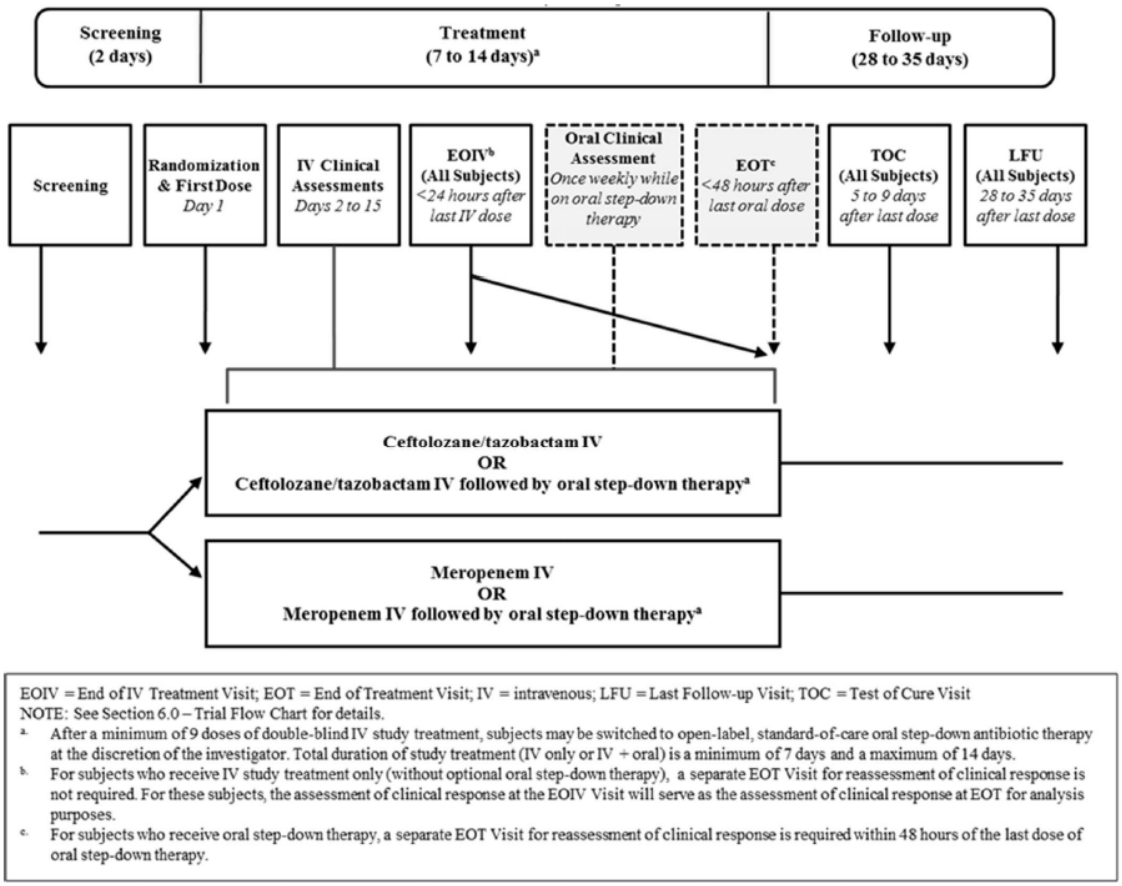
d- Some literature supports a higher MERO dosage (up to 30 mg/kg q8h) for participants 14 days to <3 months of age; therefore, MERO dosing up to 30 mg/kg q8h could be used for participants 14 days to <3 months of age at the investigator's discretion.

The primary objective of Study P034 was to evaluate the safety and tolerability of C/T compared with MERO. Secondary objectives were to evaluate the efficacy of C/T compared with MERO for clinical response at the EOT and test of cure (TOC) visits and per-participant microbiological response at the EOT and TOC visits.

Data from this study were pooled with the companion phase 2 safety and efficacy study of C/T plus MTZ in pediatric participants with cIAI to allow for an adequately sized safety database, and both studies used MERO as the comparator. A combined sample size of 240 participants was planned to be enrolled across P034 and P035. However, due to enrollment challenges in reaching age-group, disease-state, and/or country-level enrollment targets, the Applicant amended the protocols to lower the target sample size; a total of 228 participants were enrolled across both studies (134 participants in P034 and 94 participants in P035).

After a 2-day screening period, participants were randomized and received their first dose on Day 1. Participants received either IV + oral treatment or IV only treatment for a total of 7 to 14 days. After a minimum of 9 doses of double-blind treatment, participants could be switched to open-label, standard-of-care oral step-down antibiotic therapy. The end of IV treatment visit (EOIV) occurred within 24 hours of the last IV dose. This visit also served as an end of treatment (EOT) visit for participants who received IV only treatment without optional oral step-down (i.e. a separate assessment was not performed at the EOT Visit). However, a separate EOT visit did occur within 48 hours of the last oral dose for those participants receiving IV + oral treatment. For all participants, the TOC visit occurred 5 to 9 days after the last dose. Clinical and microbiological assessments were performed at the EOIV, EOT, and TOC visits. See Figure 4 for further details on the study design.

**Figure 4: Study Design (Study P034)**




EOIV = End of IV Treatment Visit; EOT = End of Treatment Visit; IV = intravenous; LFU = Last Follow-up Visit; TOC = Test of Cure Visit
NOTE: See Section 6.0 – Trial Flow Chart for details.

a. After a minimum of 9 doses of double-blind IV study treatment, subjects may be switched to open-label, standard-of-care oral step-down antibiotic therapy at the discretion of the investigator. Total duration of study treatment (IV only or IV + oral) is a minimum of 7 days and a maximum of 14 days.
b. For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate EOT Visit for reassessment of clinical response is not required. For these subjects, the assessment of clinical response at the EOIV Visit will serve as the assessment of clinical response at EOT for analysis purposes.
c. For subjects who receive oral step-down therapy, a separate EOT Visit for reassessment of clinical response is required within 48 hours of the last dose of oral step-down therapy.

**Source: CSR Figure 9-1**

**Reviewer Comments**: *In general, it is recommended that follow-up assessments are measured at a fixed point from the time to randomization rather than from the time after the last dose because the latter assessment can lead to treatment differences in the duration of study therapy related to efficacy. Note, however, that there were no substantial differences in treatment exposure between study arms in Study P034. The mean number of days of overall treatment received among treated participants was 8.2 days in the C/T and 8.0 days in the MERO arm.*

**Study Endpoints**

The primary endpoints were AEs, laboratory data, and vital signs based on the All Participants as Treated (APaT) population. Secondary endpoints were the clinical success rate at the EOT and TOC visits, defined as the proportion of participants with a clinical response of cure; and the per-participant microbiological eradication rate at the EOT and TOC visits, defined as the proportion of participants with an overall outcome of microbiological eradication, with outcome categories described in Table 8-2. Efficacy analyses were based on the mMITT, CE and

ME populations.

**Table 8-2: Clinical and Microbiological Outcome Categories (P034)**

| **Clinical Outcome** | **Definition** |
|---|---|
| Cure[1] | Complete resolution or marked improvement in signs and symptoms of the cUTI or return to preinfection signs and symptoms, such that no further antibiotic therapy (IV or oral) is required for the treatment of the cUTI. |
| Partial improvement (only at the EOIV Visit[2] for participants who switch to step-down therapy) | Partial resolution of signs and symptoms of the cUTI such that no further IV antibiotic therapy is required for the treatment of the cUTI; however, additional oral step-down therapy is required. |
| Failure | Any of the following is considered a clinical outcome of failure:<br>• Persistence or reappearance of 1 or more sign or symptom of infection that requires alternative nonstudy treatment for the current cUTI<br>• New signs or symptoms of infection that require alternative nonstudy treatment for the treatment of a cUTI due to an appropriate gram-negative uropathogen<br>• Requirement of antibiotic therapy beyond the protocol-defined treatment duration of 14 days<br>• Death related to cUTI |
| Indeterminate | Trial data are not available for evaluation of efficacy for any reason, including death during the trial period unrelated to the cUTI or extenuating circumstances, which preclude classification as cure, partial improvement, or failure (e.g., participant is lost to follow-up). |
| **Microbiological Outcome[3]** | **Definition** |
| **Eradication[4]** | A postbaseline urine culture shows all uropathogens found at baseline at $\geq 10^5$ CFU/mL are reduced to $<10^4$ CFU/mL. |
| **Persistence** | A postbaseline urine culture shows the uropathogen(s) found at baseline at $\geq 10^5$ CFU/mL persist(s) at $\geq 10^4$ CFU/mL. |
| **Indeterminate** | No appropriate urine culture result available. |

**Source: Applicant Table from Section 9.5 of CSR**

1- Clinical success rate was defined at the EOT and TOC visits as the proportion of participants in the analysis population who had a clinical response of "cure."

2- The clinical success rate at the EOIV visit was defined as the proportion of participants in the analysis population who had a clinical response of "cure" or "partial improvement." This definition included "partial improvement" to accommodate those with partial improvement switched to oral step-down therapy at this time point. For participants who received IV study treatment only (without optional oral step-down therapy), a separate assessment was not performed at the EOT Visit; the EOIV visit served as the EOT Visit.

3- The per-pathogen microbiological outcome was determined for each uropathogen isolated by the Applicant from a baseline study-qualifying culture.

4- To have a per-participant microbiological response of eradication, each baseline pathogen must have had a microbiological response of eradication. Eradication is considered a favorable microbiological response.

**Reviewer Comments:** *This review primarily considers the mMITT population for efficacy*

*analyses. Analyses in the CE and ME populations can involve biases associated with post-baseline exclusions which may be related to the treatment received.*

**Statistical Analysis Plan**

Analysis Populations

- mMITT Population: subset of All Randomized Participants who received any amount of study treatment and had at least 1 causative uropathogen from a study-qualifying baseline urine culture. Participants were categorized based on the IV study treatment they were randomized to.
- CE population: subset of mMITT participants who adhered to study procedures and had an evaluable clinical outcome at the visit of interest; participants with an indeterminate clinical outcome were excluded from the CE population. Although collection of a urine culture was required at the visit of interest, an interpretable urine culture result was not required to be included in the CE population.
- ME population: subset of participants in the CE population who had an interpretable urine culture at the visit of interest.

**Reviewer Comments:** *We generally recommend that the mMITT population include only treated subjects with a causative uropathogen that is susceptible to both study drugs as this would allow for more appropriate comparisons. However, among participants included in the mMITT of Study P034, nearly all baseline gram-negative qualifying pathogens were susceptible to both C/T and MERO (91/92 (98.9%) susceptible to C/T and 91/94 (96.8%) susceptible to MERO).*

Methodology

To address the primary safety objective, the percentage of participants with any AE, any SAE, any study treatment-related AE, any study treatment-related SAE were evaluated as well as the percentage of participants discontinuing due to an AE. AEs (specific preferred terms), system organ classes, or values outside the local laboratory's reference range with a frequency of ≥ 2 participants in the comparator group (≥ 6 participants in the experimental group due to 3:1 randomization) which was the minimum number of participants to detect any differences between the groups. The 95% confidence intervals (CIs) are provided for between-treatment differences in the percentage of participants with events; these analyses were performed using the unstratified Miettinen and Nurminen (M&N) method (1985), an unconditional, asymptotic method.

To address the secondary objectives, a 2-sided 95% CI based on the M&N method and stratified by age group was provided to evaluate (1) the treatment differences for clinical success at the EOT and TOC visits and (2) per-participant microbiological eradication at the EOT and TOC visits.

**Protocol Amendments**

The protocol amendments reflect the Applicant's prior submissions regarding changes to the protocols (SDN 336, 337 and 340) under IND 104490.

On May 1, 2020, the Applicant submitted a request for Agency agreement regarding proposed amendments to these PMR study protocols (SDN 336). The modifications were designed to expedite enrollment and completion of the pediatric studies. The proposed update included:

- Removal of the requirement that at least 4 subjects be enrolled in each study for Group 4 (3 months to <2 years) and Group 5 (birth to <3 months)

On May 5, 2020, the Division sent an IR requesting the Applicant's rationale on why PK (b) (4) As an alternative option, the Division recommended that the Applicant consider enrolling a minimum of 3 subjects in each group.

On May 12, 2020, the Applicant submitted a response (SDN 337) outlining the proposed approach for extrapolating the potential effect of age on ceftolozane and tazobactam PK in cIAI patients <2 years of age (group 4 and group 5) using a population PK modeling approach. The Division sent a correspondence on May 14, 2020 accepting the Applicant's proposal of updating the Group 4 and Group 5 enrollment targets.

On June 19, 2020, the Applicant submitted a proposal to end enrollment early in P034 and P035, with the currently enrolled combined total number of 222 subjects (representing a decrease from the target overall minimum enrollment of 240 subjects), which would also reflect a decrease in the combined target minimum enrollment for Age Groups 3 (from 72 to 57 subjects) and 5 (from 24 to 21 subjects).

**Reviewer Comment:** *The amended protocol P034-03 was considered to be acceptable.*

### 8.1.2. Study Results of P034

**Compliance with Good Clinical Practices**

Per the Applicant, all trials were undertaken in accordance with standard operating procedures at the time of clinical conduct, which complied with the principles of Good Clinical Practice. All trials were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and its amendments in force at the time of the trial. All trials were approved by Ethics Committees or Institutional Review Boards and Competent authorities. Informed consent was obtained for all subjects.

**Financial Disclosure**

The Applicant submitted the required Financial Disclosure information. See section 15.1 for further information.

**Patient Disposition**

Patient disposition is described in **Table 8-3** and **Table 8-4**. In the C/T and MERO arms, respectively, nearly all participants received study treatment (99% and 100%) and completed the study (96% and 100%). Approximately 70% and 73% of randomized participants qualified for inclusion into the mMITT population. There were no major imbalances noted with respect to study completion rates and the percentages of participants included in each of the analysis populations defined. However, a slightly larger percentage of participants in the MERO arm were microbiologically evaluable at the TOC visit (51.5% versus 43.6%).

**Table 8-3: Patient Disposition (All Randomized Population, Study P034)**

| | C/T | MERO |
|---|---|---|
| Patients in population | 101 (100%) | 33 (100%) |
| Completed study | 97 (96.0%) | 33 (100%) |
| Discontinued | 4 (4.0%) | 0 |
| Withdrawal by Parent/Guardian | 3 (3.0%) | 0 |
| Other | 1 (1.0%) | 0 |

**Source: Partially Adapted from CSR Table 14.1-1**

**Table 8-4: Patient Disposition by Defined Analysis Populations (All Randomized, P034)**

| Population | C/T | MERO |
|---|---|---|
| All Randomized | 101 (100%) | 33 (100%) |
| As Treated | 100 (99.0%) | 33 (100%) |
| Microbiological Modified Intent-to-Treat (mMITT) | 71 (70.3%) | 24 (72.7%) |
| Clinically Evaluable at EOIV | 67 (66.3%) | 21 (63.6%) |
| Clinically Evaluable at EOT | 66 (65.3%) | 21 (63.6%) |
| Clinically Evaluable at TOC | 48 (47.5%) | 17 (51.5%) |
| Microbiologically Evaluable at EOIV | 60 (59.4%) | 21 (63.6%) |
| Microbiologically Evaluable at EOT | 58 (57.4%) | 20 (60.6%) |

| | | |
|---|---|---|
| Microbiologically Evaluable at TOC | 44 (43.6%) | 17 (51.5%) |

**Source: Partially Adapted from CSR Table 14.1-7**

### Protocol Violations/Deviations

**Table 8-5** shows the important protocol violations occurring in the C/T and MERO study arms in the APaT population of Study P034. Protocol deviations occurred more frequently in the C/T study arm versus the MERO study arm, 29 (29.0%) versus 7 (21.2%). Protocol deviations relating to inclusion/exclusion criteria and study interventions were lower in the C/T arm, 10 (10.0%) versus 6 (18.2%) and 5 (5.0%) versus 3 (9.1%), respectively, while protocol deviations relating to study procedures were higher in the C/T study arm, 18 (18.0%) versus 0. Reasons for the treatment imbalances for these categories of study deviations are unclear.

**Table 8-5 Important Protocol Deviations (APaT population, Study P034)**

| | **C/T** N=100 | **MERO** N=33 |
|---|---|---|
| **One or more important protocol deviations** | 29 (29.0) | 7 (21.2) |
| **Inclusion/exclusion Criteria**<br>Did not meet inclusion criteria 2, 5 -7, 8, 9 or exclusion criteria 3, 4, 6-14 as defined in the protocol. | 10 (10.0) | 6 (18.2) |
| **Informed Consent**<br>No documented inform consent as required per age group | 1 (1.0) | 0 |
| **Prohibited Medications**<br>Received ≥ 1 dose of gram negative systemic antibiotics (except for 1 dose of prophylactive antibiotics) | 1 (1.0) | 1 (3.0) |
| **Safety Reporting**<br>Missed scheduled safety AE assessment | 1 (1.0) | 0 |
| **Any Study Intervention Deviation** | 5 (5.0) | 3 (9.1) |
| Began oral step down therapy > 24 hours after completion of IV study medication | 0 | 1 (3.0) |
| Received <80 or >120% of individual dose | 1 (1.0) | 0 |
| Was administered improperly stored study medication that was deemed unacceptable for use | 2 (2.0) | 2 (6.1) |
| Inadvertently unblinded during trial | 1 (1.0) | 2 (6.1) |
| Study drug infused over >30min or >90 min | 2 (2.0) | 0 |
| **Any Trial Procedure Deviation** | 18 (18.0) | 0 |
| An unnecessary study visit occurred where invasive procedures were performed. | 2 (2.0) | 0 |
| EOIV, EOT, TOC, LFU, or oral safety assessment (when applicable) was 3 or more days outside of window. | 8 (8.0) | 0 |
| No urine culture was obtained where required by protocol. | 10 (10.0) | 0 |

| | | |
|---|---|---|
| Participant missed scheduled EOIV, EOT or TOC clinical outcome assessment or assessment not done. | 2 (2.0) | 0 |

**Source: Partially Adapted from CSR Table 14.1-3**
Note: Every participant is counted a single time for each applicable row and column.

### Demographic and Baseline Characteristics

**Table 8-6** shows the demographic and baseline characteristics for participants included in the mMITT population of Study P034. Given the high degree of variability resulting from only 24 patients being included in the MERO arm, there were some imbalances in baseline characteristics between the treatment arms. For example, the median age of participants was higher in the C/T arm (median age of 2.7 years) compared to the MERO arm (median age of 1.6 years). In addition, the C/T arm included a smaller percentage of participants from the North American region compared to the MERO arm, 7 (9.9%) versus 4 (16.7%).

**Table 8-6: Demographic and Baseline Characteristics (mMITT, P034)**

| Demographic Parameters | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) |
|---|---|---|
| **Sex** | | |
| Male | 31 (43.7) | 9 (37.5) |
| Female | 40 (56.3) | 15 (62.5) |
| **Age Group** | | |
| 12 to <18 years | 10 (14.1) | 2 (8.3) |
| 6 to <12 years | 13 (18.3) | 4 (16.7) |
| 2 to <6 years | 14 (19.7) | 6 (25.0) |
| 3 months to <2 years | 20 (28.2) | 6 (25.0) |
| 0 to < 3 months | 14 (19.7) | 6 (25.0) |
| **Race** | | |
| Asian | 1 (1.4) | 0 (0.0) |
| White | 70 (98.6) | 24 (100.0) |
| **Ethnicity** | | |
| Hispanic or Latino | 6 (8.5) | 4 (16.7) |
| Not Hispanic or Latino | 55 (77.5) | 19 (79.2) |
| Not reported | 1 (1.4) | 0 (0.0) |
| Unknown | 9 (12.7) | 1 (4.2) |
| **Region** | | |
| North America | 7 (9.9) | 4 (16.7) |
| Europe | 64 (90.1) | 20 (83.3) |

**Source: Partially Adapted from CSR Table 14.1-8**

Age differences between C/T and MERO for each age group category are shown in **Table 8-7**. Participants in the age groups of 3 months to 2 years and 2 years to 6 years were observed to be older in the C/T arm versus the MERO arm (medians of 0.94 versus 0.49 years and 3.63 versus 2.84 years, respectively).

**Table 8-7: Comparison of Ages by Age Group and Treatment Group (mMITT, P034)**

| | **Group 1: 12 to <18y** | **Group 2: 6 to <12y** | **Group 3: 2 to <6y** | **Group 4: 3mo to <2y** | **Group 5: 0 to < 3mo** | **Total** |
|---|---|---|---|---|---|---|
| **C/T** | N=10 | N=13 | N=14 | N=20 | N=14 | N=71 |
| Mean (yrs) | 14.96 | 8.40 | 3.73 | 0.91 | 0.12 | 4.66 |
| Std | 1.65 | 1.78 | 0.90 | 0.41 | 0.05 | 5.21 |
| Median | 15.20 | 7.63 | 3.63 | 0.94 | 0.10 | 2.68 |
| Range | 12.16, 17.32 | 6.06, 11.95 | 2.32, 5.76 | 0.26, 1.69 | 0.06, 0.21 | 0.06, 17.32 |
| **MERO** | N=2 | N=4 | N=6 | N=6 | N=6 | N=24 |
| Mean (yrs) | 16.66 | 8.74 | 3.17 | 0.61 | 0.14 | 3.82 |
| Std | 1.54 | 1.66 | 1.10 | 0.36 | 0.07 | 5.06 |
| Median | 16.66 | 9.13 | 2.84 | 0.49 | 0.14 | 1.64 |
| Range | 15.56, 17.75 | 6.41, 10.30 | 2.05, 4.64 | 0.29, 1.23 | 0.03, 0.24 | 0.03, 17.45 |

**Source: Partially Adapted from CSR Table 14.1-8**

**Other Baseline Characteristics**

**Table 8-8** compares other baseline characteristics between treatments in the mMITT population. Given the limited number of patients in the MERO arm, some imbalances were observed. For example, participants in the C/T arm were slightly taller than in the MERO arm (median height of 92.0 cm versus 80.5 cm) and weighed more (median weight of 13.0 kg versus 10.4 kg), which is consistent with their having a higher median age (2.68 vs. 1.64 years, **Table 8-7**). In addition, a smaller percentage of participants in the C/T arm had bacteremia at baseline, 3 (4.2%) versus 3 (12.5%).

**Table 8-8: Other Baseline characteristics (mMITT, P034)**

| Baseline Parameters | **C/T** N=71 n (%) | **MERO** N=24 n (%) |
|---|---|---|
| **Baseline Diagnosis** | | |
| Pyelonephritis | 60 (84.5) | 19 (79.2) |
| cLUTI | 11 (15.5) | 5 (20.8) |
| **Bacteremia at Baseline** | | |
| Yes | 3 (4.2) | 3 (12.5) |
| No | 68 (95.8) | 21 (87.5) |
| **Urine sample collected via urinary catheter** | | |

| | | |
|---|---|---|
| Yes | 29 (40.8) | 9 (37.5) |
| No | 42 (59.2) | 15 (62.5) |
| **Baseline eGFR** | | |
| eGFR ≥ 80 | 48 (67.6) | 16 (66.7) |
| eGFR ≥ 50 to < 80 | 23 (32.4) | 7 (29.2) |
| eGFR ≥ 30 to < 50 | 0 (0.0) | 1 (4.2) |
| **Failure of Prior Therapy** | | |
| Yes | 3 (4.2) | 0 (0.0) |
| No | 68 (95.8) | 24 (100.0) |
| **Height (cm)** | | |
| Mean (SD) | 98.6 (37.1) | 91.7 (35.0) |
| Median (range) | 92.0 (51 to 172) | 80.5 (55 to 163) |
| **Weight (kg)** | | |
| Mean (SD) | 19.4 (17.2) | 16.7 (14.7) |
| Median (range) | 13.0 (2.6 to 75.3) | 10.4 (3.8 to 54.0) |

**Source: Partially Adapted from CSR Table 14.1-8**
cLUTI = complicated lower urinary tract infections

### Treatment Compliance and Concomitant Medications

**Table 8-9** shows the overall treatment compliance for the C/T and MERO arms in the mMITT population of Study P034. These comparisons show that treatment compliance was generally high in both study arms with all participants having at least 80% compliance. The percentages of participants with > 80% to 100% compliance and > 100% compliance were also similar between treatment arms.

**Table 8-9: Treatment Compliance (mMITT, P034)**

| | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) |
|---|---|---|
| **Overall Treatment Compliance** | | |
| ≤ 80% | 0 (0.0) | 0 (0.0) |
| > 80% to ≤ 100% | 48 (67.6) | 16 (66.7) |
| > 100% | 23 (32.4) | 8 (33.3) |
| **Summary Statistics for Overall Treatment Compliance** | | |
| Mean (SD) | 99.8 (2.0) | 98.9 (3.0) |
| Median (range) | 100.0 (90.6 to 105.5) | 100.0 (90.5 to 102.4) |

**Source: Partially Adapted from CSR Table 14.1-37**

**Table 8-10** shows the use of concomitant medications among subjects included in the mMITT population of Study P034. The percentage of participants using one or more concomitant medications through the TOC visit was greater in the C/T arm compared to the MERO arm, 23

(32.4%) versus 7 (29.2%). The most common antibacterial for systemic use was a combination of sulfamethoxazole and trimethoprim which was used in 10 (14.1%) and 2 (8.3%) of participants in the C/T and meropenem arms, respectively. Nitrofurantoin was also relatively common, being used in 6 (8.5%) of participants in the C/T arm.

**Table 8-10: Participants with Concomitant Antibacterial Use through TOC Visit (mMITT, P034)**

| | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) |
|---|---|---|
| **Concomitant Antibacterials for systemic use** | 23 (32.4) | 7 (29.2) |
| Amikacin | 1 (1.4) | 0 (0.0) |
| Amikacin Sulfate | 1 (1.4) | 0 (0.0) |
| Amoxicillin Trihydrate; Clavulanate Potassium | 1 (1.4) | 1 (4.2) |
| Ampicillin Sodium; Sulbactam Sodium | 1 (1.4) | 0 (0.0) |
| Cefaclor | 1 (1.4) | 0 (0.0) |
| Cefixime | 0 (0.0) | 1 (4.2) |
| Cefotaxime Sodium | 1 (1.4) | 0 (0.0) |
| Ceftriaxone | 0 (0.0) | 2 (8.3) |
| Furazidin | 0 (0.0) | 1 (4.2) |
| Meropenem | 1 (1.4) | 0 (0.0) |
| Nitrofurantoin | 6 (8.5) | 0 (0.0) |
| Sulfadimidine; Trimethoprim | 1 (1.4) | 0 (0.0) |
| Sulfamethoxazole; Trimethoprim | 10 (14.1) | 2 (8.3) |
| Sultamicillin | 2 (2.8) | 0 (0.0) |

**Source: Partially Adapted from CSR Table 14.1-36**
This table includes non-study antibiotic medications taken between the date of the first dose of IV study medication and the TOC visit. It also includes those medications stopped on the same date as the first dose of IV study medication without a confirmed stop time, or started on the same date as the TOC visit date without a confirmed start time.

**Efficacy Results – Secondary Efficacy Endpoints**

The primary endpoints of Study P034 were AEs, laboratory data, and vital signs in the APaT population. Efficacy endpoints in Study P034, specified as secondary, included clinical success rates and per-patient microbiological success rates at EOT and TOC in the mMITT, CE and ME populations. These endpoints were intended to provide point estimates of the efficacy of each treatment regimen since the study was not powered for formal hypothesis testing of between treatment group comparisons.

**Reviewer Comments***: As noted above, this review primarily considers the mMITT population for efficacy analyses. Analyses in the CE and ME populations can involve biases associated with post-baseline exclusions which may be related to the treatment received.*

**Table 8-11** shows the clinical response rates at the EOT and TOC visits for participants included in the mMITT population. Success rates at EOT and TOC were high in both study arms but were numerically lower in the C/T arm compared to the MERO arm.

At the EOT visit, clinical success rates in the C/T arm versus the MERO arm were 67/71 (94.4%) versus 24/24 (100%), an adjusted difference of -5.6% (95% CI: -14.1%, 8.9%). Of the 4 (5.6%) participants counted as failures at EOT in the C/T arm, 2 were observed failures and 2 were observed indeterminates.

At the TOC visit, clinical success rates in the C/T arm versus the MERO arm were 63/71 (88.7%) versus 23/24 (95.8%), an adjusted difference of -7.3% (95% CI: -18.0%, 10.1%). Of the 8 (11.3%) participants counted as failures at TOC in the C/T arm, 4 were observed failures and 4 were indeterminates (observed or imputed). Comparisons of the observed failure rate (5.6% versus 4.2%) which excludes indeterminates was noted as being less pronounced than comparisons of the failure rate (11.3% versus 4.2%).

**Table 8-11: Clinical Response at EOT and TOC Visits (mMITT, P034)**

| | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) | **Difference (95%)**<br>(C/T – MERO)<br>(%) |
|---|---|---|---|
| **EOT Visit** | | | |
| Success | 67 (94.4) | 24 (100) | -5.6 (-14.1, 8.9) |
| Failure | 4 (5.6) | 0 | |
| Observed Failure | 2 (2.8) | 0 | |
| Observed Indeterminate | 2 (2.8) | 0 | |
| **TOC Visit** | | | |
| Success | 63 (88.7) | 23 (95.8) | -7.3 (-18.0, 10.1) |
| Failure | 8 (11.3) | 1 (4.2) | |
| Observed Failure | 4 (5.6) | 1 (4.2) | |
| Observed Indeterminate | 1 (1.4) | 0 | |
| Imputed Indeterminate[1] | 3 (4.2) | 0 | |

**Source: Partially Adapted from CSR Table 11-1**
1- Imputed indeterminate clinical response includes participants who had a clinical cure, partial improvement or indeterminate at the previous visit(s) and had missing clinical response at the specific visit.
Note: The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights.

**Table 8-12** shows the per-participant microbiological response rates at the EOT and TOC visits for participants included in the mMITT population of Study P034. Eradiation rates at EOT and TOC were high in both study arms but were numerically lower in the C/T arm compared to the MERO arm.

At the EOT visit, eradication rates in the C/T arm versus the MERO arm were 66/71 (93.0%) versus 23/24 (95.8%), an adjusted difference of -3.4% (95% CI: -12.7%, 13.4%). Of the 5 (7.1%)

participants counted as having persistence at EOT in the C/T arm, 1 had observed persistence while the other 4 were indeterminates (imputed). The 1 participant counted as having persistence in the MERO arm was an observed indeterminate.

At the TOC visit, eradication rates in the C/T arm versus the MERO arm were 60/71 (84.5%) versus 21/24 (87.5%), an adjusted difference of -3.0% (95% CI: -17.1%, 17.4%). Of the 11 (15.5%) participants counted as having persistence at TOC in the C/T arm, 4 had observed persistence while the other 7 were imputed indeterminates. Of the 3 (12.5%) participants counted as having persistence at TOC in the MERO arm, all 3 had observed persistence. Comparisons of the observed persistence rate (5.6% versus 12.5%) which excludes indeterminates was noted as being more favorable in the C/T arm while comparisons of the persistence rate (15.5% versus 12.5%) favored the MERO arm.

**Table 8-12: Per-Participant Microbiological Outcome at EOT and TOC Visits (mMITT, P034)**

| | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) | **Difference (95% CI)**<br>(C/T – MERO)<br>(%) |
|---|---|---|---|
| **EOT Visit** | | | |
| Eradication | 66 (93.0) | 23 (95.8) | -3.4 (-12.7, 13.4) |
| Persistence | 5 (7.0) | 1 (4.2) | |
| Observed Persistence | 1 (1.4) | 0 | |
| Observed Indeterminate | 0 | 1 (4.2) | |
| Imputed Indeterminate | 4 (5.6) | 0 | |
| **TOC Visit** | | | |
| Eradication | 60 (84.5) | 21 (87.5) | -3.0 (-17.1, 17.4) |
| Persistence | 11 (15.5) | 3 (12.5) | |
| Observed Persistence | 4 (5.6) | 3 (12.5) | |
| Imputed Indeterminate | 7 (9.9) | 0 | |

**Source: Partially Adapted from CSR Table 11-2**
The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights.

Clinical success rates and per-participant microbiological eradication rates by age group (i.e., between-treatment groups within each age group and across age groups) were generally consistent with the overall clinical success rates by treatment group. The per-participant microbiological eradication rates in the ME population were also generally consistent with those reported in the mMITT populations for both the TOC and EOT visits.

**Reviewer Comments:** *There are some concerns with the lower clinical success rates observed in the C/T arm in comparison to the* MERO *arm especially since a similar trend was observed in Study P035 for the cIAI indication. However, as shown in* **Table 8-31***, clinical success rates in the C/T arm were not substantially below what would be expected based on the adults studies. In*

*addition, much of the difference in clinical success rates at EOT and TOC was due to higher rates of indeterminate outcomes in the C/T arm.*

**Data Quality and Integrity**

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

**Efficacy Results – Secondary and other relevant endpoints**

The secondary efficacy endpoints of clinical success and per-participant microbiological response in the mMITT population described above were considered to be most relevant. The exploratory endpoint of composite response (clinical response and per-participant microbiological response) was also of interest.

As shown in **Table 8-13**, the composite success rates at the TOC visit in the mMITT population were lower in the C/T arm versus the MERO arm (80.3% versus 87.5%). Similar treatment differences in composite success rates were observed at the EOIV and EOT visits.

**Table 8-13: Composite Success Rates (mMITT, P034)**

| **Composite Success Rates (clinical success and microbiological success)** | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) |
|---|---|---|
| **EOIV Visit** | | |
| Success | 65 (91.5) | 24 (100) |
| Failure | 6 (8.5) | 0 |
| **EOT Visit** | | |
| Success | 63 (88.7) | 23 (95.8) |
| Failure | 8 (11.3) | 1 (4.2) |
| **TOC Visit** | | |
| Success | 57 (80.3) | 21 (87.5) |
| Failure | 14 (19.7) | 3 (12.5) |

**Source: Partially Adapted from CSR Tables 14.2-29, 14.2-30 and 14.2-31**

Exploratory efficacy endpoints defined in the protocol also included clinical response and per-participant microbiological response at the EOIV visit. Treatment differences for these endpoints at the EOIV visit (**Table 8-14**) were consistent with the corresponding differences observed at the EOT and TOC visits (**Table 8-11** and **Table 8-12)**.

**Table 8-14: Clinical Response and Per-Participant Microbiological Response at the EOIV Visit (mMITT, P034)**

| | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) | **Difference (95% CI)**<br>(C/T – MERO)<br>(%) |
|---|---|---|---|
| **Clinical Response at EOIV Visit** | | | |
| Success | 67 (94.4) | 24 (100) | -5.6 (-14.1, 8.9) |
| Partial Improvement | 50 (70.4) | 20 (83.3) | |
| Cure | 17 (23.9) | 4 (16.7) | |
| Failure | 4 (5.6) | 0 | |
| Observed Failure | 2 (2.8) | 0 | |
| Observed Indeterminate | 2 (2.8) | 0 | |
| **Per-Participant Microbiological Response at EOIV Visit** | | | |
| Eradication | 68 (95.8) | 24 (100) | -3.6 (-11.2, 11.1) |
| Persistence | 3 (4.2) | 0 | |
| Imputed Indeterminate | 3 (4.2) | 0 | |

**Source: Partially Adapted from CSR Tables 14.2-19 and14.2-21**
The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights.

Other exploratory secondary endpoints included the per-pathogen microbiological response at the EOIV, EOT and TOC visits in the mMITT population. Findings for these endpoints at the TOC visit are shown in **Table 8-15**. From this table, a large percentage of participants are shown to have pathogens of the Enterobacterales order, most commonly *Escherichia coli*. There were no clear trends regarding treatment differences in eradication rates for specific pathogens or pathogen groups. However, per-pathogen eradication rates in participants with *Pseudomonas aeruginosa* at baseline did appear to be lower in the C/T arm versus the MERO arm, (3/5 (60.0%) versus 2/2 (100%)). Note that these comparisons, as well as comparisons for many other specific pathogens, are limited by small numbers.

**Table 8-15: Per-Pathogen Microbiological Outcome at the TOC Visit (mMITT, P034)**

| | **C/T**<br>N=71<br>n (%) | **MERO**<br>N=24<br>n (%) |
|---|---|---|
| **Aerobic Gram-negative** | N=71 | N=24 |
| Eradication, n | 61 (85.9) | 21 (87.5) |
| Persistence, n | 11(15.5) | 3 (12.5) |
| **Enterobacterales** | N=66 | N=22 |
| Eradication, n | 58 (87.9) | 19 (86.4) |
| Persistence, n | 9 (13.6) | 3 (13.6) |
| ***Enterobacter cloacae complex*** | N=3 | N=0 |
| Eradication, n | 3/3 (100) | 0 |
| ***Escherichia Coli*** | N=53 | N=21 |

| | | |
|---|---|---|
| Eradication, n | 45 (84.9) | 18 (85.7) |
| Persistence, n | 8 (15.1) | 3 (14.3) |
| ***Klebsiella pneumoniae*** | N=6 | N=1 |
| Eradication, n | 6 (100) | 1 (100) |
| ***Proteus mirabilis*** | N=2 | N=1 |
| Eradication, n | 2 (100) | 1 (100) |
| ***Pseudomonas aeruginosa*** | N=5 | N=2 |
| Eradication, n | 3 (60.0) | 2 (100) |
| Persistence, n | 2 (40.0) | 0 |

**Source: Partially Adapted from CSR Table 14.2-23**
N= Number of participants in specific population of pathogen or pathogen category
n=Number of participants in specific category
Participants with missing/indeterminate microbiological outcome counted as having 'persistence'

**Durability of Response**

Efficacy data beyond the TOC visit were not collected. There were no concerns related to the durability of the response through the TOC Visit. Treatment differences in clinical response rates between the C/T and MERO arms did not indicate an unfavorable trend across the EOIV, EOT and TOC visits.

**Persistence of Effect**

The persistence of effect of C/T is not anticipated to be of long duration, due to its rapid elimination (approximately 2 to 3 hours for ceftolozane and 1 hour for tazobactam).

**Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

There were no additional secondary or exploratory COA (PRO) endpoints defined.

**Additional Analyses Conducted on the Individual Trial**

Additional analyses conducted on Study P034 included subgroup analyses of clinical cure rates at the TOC visit for various categories. **Table 8-16** shows the proportions of subjects who were clinical cures at TOC who fell into these subgroups. There were no notable findings when considering clinical cure rates in these subgroups, however, slightly more pronounced differences in cure rates favoring MERO were observed in participants with complicated lower urinary tract infections (cLUTI) at baseline (63.6% versus 100%), participants with a urine sample not collected via urinary catheter (83.3% versus 100%) and participants with no prior antibiotic use (80.0% versus 100%). Note the comparisons between treatment arms by subgroup were limited due to the small numbers of participants in the MERO arm.

**Table 8-16: Subgroup Analyses of Participants Achieving Clinical Cure at the TOC Visit (mMITT, P034)**

| | **C/T**<br>N=71<br>n/N (%) | **MERO**<br>N=24<br>n/N (%) |
|---|---|---|
| **Sex** | | |
| Male | 28/31 (90.3) | 8/9 (88.9) |
| Female | 35/40 (87.5) | 15/15 (100) |
| **Region** | | |
| North America | 7/7 (100) | 3/4 (75.0) |
| Europe | 56/64 (87.5) | 20/20 (100) |
| **Baseline Diagnosis** | | |
| Pyelonephritis | 56/60 (93.3) | 18/19 (94.7) |
| cLUTI | 7/11 (63.6) | 5/5 (100) |
| **Age Category** | | |
| 12 to < 18 years | 10/10 (100) | 2/2 (100) |
| 6 to < 12 years | 10/13 (76.9) | 4/4 (100) |
| 2 to < 6 years | 12/14 (85.7) | 6/6 (100) |
| 3 months to < 2 years | 18/20 (90.0) | 5/6 (83.3) |
| 0 to < 3 months | 13/14 (92.9) | 6/6 (100) |
| **Duration of IV Treatment** | | |
| < 7 days | 44/49 (89.8) | 15/16 (93.8) |
| ≥ 7 days | 19/22 (86.4) | 8/8 (100) |
| **Bacteremia at Baseline?** | | |
| Yes | 2/3 (66.7) | 3/3 (100) |
| No | 61/68 (89.7) | 20/21 (95.2) |
| **Urine Sample Collected via Urinary Catheter** | | |
| Yes | 28/29 (96.6) | 8/9 (88.9) |
| No | 35/42 (83.3) | 15/15 (100) |
| **Prior Antibiotic Use** | | |
| Yes | 39/41 (95.1) | 18/19 (94.7) |
| No | 24/30 (80.0) | 5/5 (100) |

cLUTI = complicated lower urinary tract infections
**Source: Partially Adapted from CSR Table 11-3**

### 8.1.3. Study P035

**Trial Design**

Study MK-7625A-035 (P035) was a phase 2, randomized, active comparator-controlled, multicenter, double-blind study evaluating the safety and efficacy of ceftolozane/tazobactam (C/T) plus MTZ versus MERO plus placebo in pediatric participants from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cIAI. Eligible participants were randomized in a 3:1 ratio to receive intravenous (IV) C/T +MTZ or MERO + placebo,

respectively, with stratification by age group (**Table 8-17**).

**Table 8-17: Dosing Regimen by Age Group, Study P035**

| IV Drug | Dose/Potency | Dose Frequency [a,b] |
|---|---|---|
| **Group 1 (12 to <18 years)** | | |
| C/T | Ceftolozane 1 g/and tazobactam 0.5 g | q8h |
| MTZ | MTZ 10 mg/kg (maximum dose 1.5 g/day) | q8h |
| MERO and placebo for MTZ | 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 2 (6 to <12 years)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MTZ | MTZ 10 mg/kg (maximum dose 1.5 g/day) | q8h |
| MERO and placebo for MTZ | 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 3 (2 to <6 years)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MTZ | MTZ 10 mg/kg (maximum dose 1.5 g/day) | q8h |
| MERO and placebo for MTZ | 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 4 (3 months to <2 years)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MTZ | MTZ 10 mg/kg (maximum dose 1.5 g/day) | q8h |
| MERO and placebo for MTZ | 20 mg/kg (maximum 1 g/dose) | q8h |
| **Group 5 (Birth[c] to <3 months)** | | |
| C/T | Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) | q8h |
| MTZ | *Participants >28 days of age:*<br>MTZ 10 mg/kg q 8 hours (maximum dose 1.5 g/day)<br>*For participants ≤28 days of age, the suggested dosing regimen is listed below; however, other site-specific standard of care MTZ dosing was permitted at the investigator's discretion.*<br>*Participants ≤28 days of age and ≤2 kg:*<br>MTZ 15 mg/kg loading dose, then 7.5 mg/kg/dose q 12 hours<br>*Participants ≤28 days of age and >2 kg:*<br>MTZ 15 mg/kg loading dose, 10 mg/kg dose q 8 hours | q8h[d] |
| MERO and placebo for MTZ | 20 mg/kg (maximum 1 g/dose)[e] | q8h |

**Source: Synopsis of CSR**

[a] Each dose of C/T or MTZ or MERO or placebo was administered as a 60-minute (±10 minutes) infusion. C/T+MTZ or MERO + placebo was to be dosed every 8 hours (±1 hour) after the previous infusion. The second IV dose had a ±4-hour window for dosing to facilitate adjustment of the dosing schedule (once every 8 hours) to be carried out throughout the dosing period.

[b] After receiving at least 9 doses of double-blind IV study treatment, participants could be switched to open-label, standard of care, oral step-down therapy at the investigator's discretion. The total duration of study treatment (IV only or IV + oral) was a minimum of 5 days and a maximum of 14 days.

[c] Birth was defined as >32 weeks gestational age and ≥7 days postnatal.

[d] Participants 7 to 28 days of age who received MTZ with a frequency other than every 8 hours were required to receive placebo at the same frequency to maintain blinding.

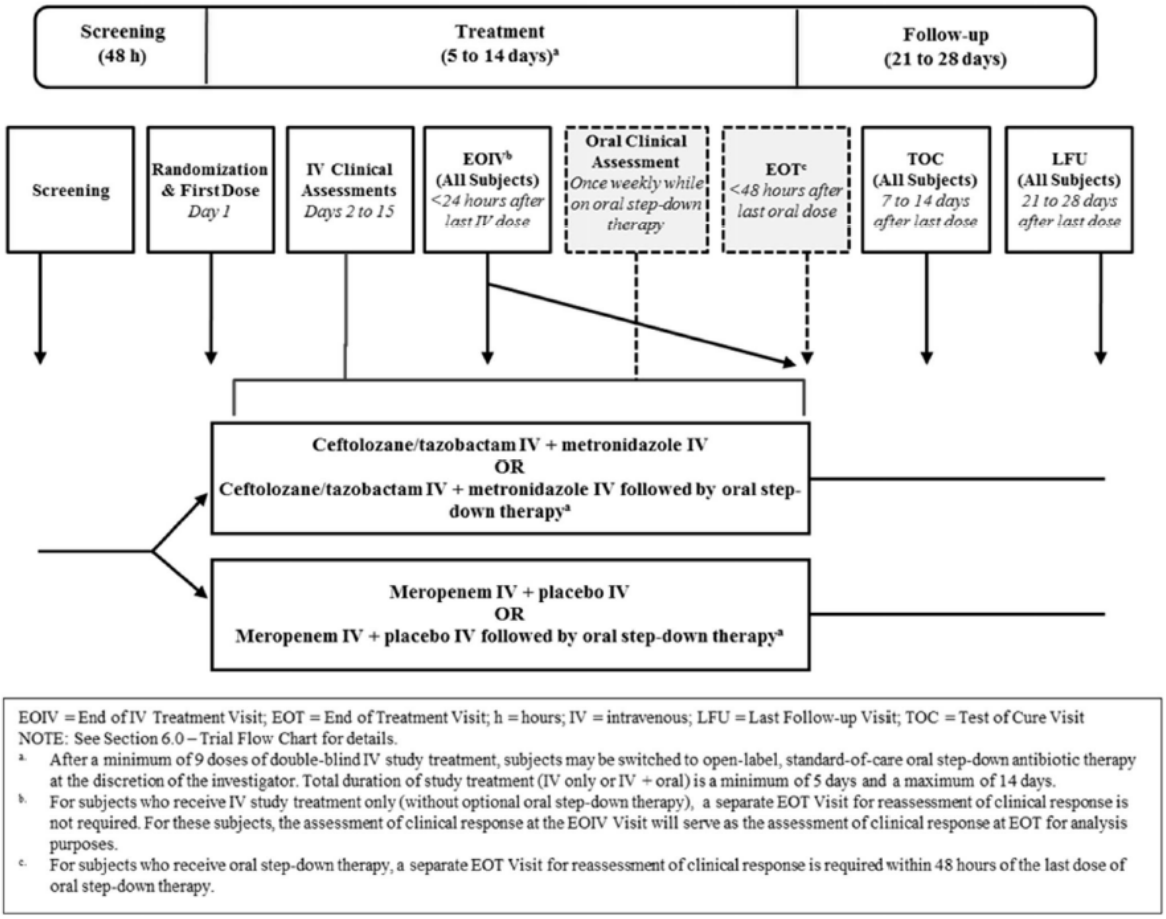
[e] Some literature supports a higher meropenem dosage (up to 30 mg/kg every 8 hours) for participants 14 days to <3 months of age; therefore, MERO dosing up to 30 mg/kg every 8 hours could be used for participants 14 days to <3 months of age at the investigator's discretion.

The primary objective of the study was to evaluate the safety and tolerability of C/T plus MTZ compared with that of MERO. Secondary objectives were to evaluate the efficacy of C/T+MTZ compared with that of MERO with respect to clinical response at the EOT and TOC visits and per-participant microbiological response at the EOT and TOC visits.

Data from this study were pooled with the companion phase 2 safety and efficacy study of C/T in pediatric participants with cUTI to allow for an adequately sized safety database; both studies used MERO as the comparator. As mentioned above, a combined sample size of 240 participants was planned to be enrolled across P034 and P035. However, due to enrollment challenges in reaching age-group, disease-state, and/or country-level enrollment targets, the Applicant amended the protocols to lower the target sample size; a total of 228 participants were enrolled across both studies (134 participants in P034 and 94 participants in P035).

After a 2-day screening period, participants were randomized and received their first dose on Day 1, participants in the C/T+MTZ arm received either IV (C/T) + IV (MTZ) + oral treatment or IV (C/T) + IV (MTZ) for total of 5 to 14 days and participants in the MERO arm received either IV (MERO) + IV (placebo) + oral treatment or IV (MERO) + IV (placebo) for total of 5 to 14 days. After a minimum of 9 doses of double-blind treatment, subjects could be switched to open-label, standard-of-care oral step-down antibiotic therapy. The EOIV visit occurred within 24 hours of the last IV dose. This visit also served as an EOT visit for participants who received IV only treatment without optional oral step-down (i.e. a separate assessment was not performed at the EOT Visit). However, a separate EOT visit did occur within 48 hours of the last oral dose for those participants receiving IV + oral treatment. For all participants, the TOC visit occurred 7 to 14 days after the last dose, and the LFU visit occurred 21 to 28 days after the last dose. Clinical and microbiological assessments were performed at the EOIV, EOT, and TOC visits. See Figure 5 for further details on the study design.

**Figure 5: Study Design (Study P035)**




EOIV = End of IV Treatment Visit; EOT = End of Treatment Visit; h = hours; IV = intravenous; LFU = Last Follow-up Visit; TOC = Test of Cure Visit
NOTE: See Section 6.0 – Trial Flow Chart for details.

a. After a minimum of 9 doses of double-blind IV study treatment, subjects may be switched to open-label, standard-of-care oral step-down antibiotic therapy at the discretion of the investigator. Total duration of study treatment (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days.
b. For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate EOT Visit for reassessment of clinical response is not required. For these subjects, the assessment of clinical response at the EOIV Visit will serve as the assessment of clinical response at EOT for analysis purposes.
c. For subjects who receive oral step-down therapy, a separate EOT Visit for reassessment of clinical response is required within 48 hours of the last dose of oral step-down therapy.

**Source: CSR Figure 9-1**

**Reviewer Comments**: *In general, it is recommended that follow-up assessments are measured at a fixed point from the time of randomization rather than from the time after the last dose of study therapy; the latter approach can lead to treatment differences in the duration of study therapy related to efficacy. Note, however, that there were no substantial differences in study treatment exposure between study arms. The mean number of days of overall treatment received among treated participants in Study P035 was 9.3 days in the C/T+MTZ arm and 9.0 days in the MERO arm.*

## Study Endpoints

The primary endpoint was the safety and tolerability of C/T+MTZ compared to MERO based on the All Participants as Treated (APaT) population. Secondary endpoints were the clinical success rate at the EOT and TOC visits, defined as the proportion of participants with a clinical response of cure; and the per-participant microbiological eradication rate at the EOT and TOC

visits, defined as the proportion of participants with an overall outcome of microbiological eradication, with outcome categories described in **Table 8-18**. Efficacy analyses were based on the mMITT, MITT, CE, and ME populations.

**Table 8-18: Clinical, Microbiological and Emergent Infection Outcome Categories (P035)**

| **Clinical Outcome** | **Definition** |
|---|---|
| Cure[1] | Complete resolution or marked improvement in signs and symptoms of the cIAI or return to preinfection signs and symptoms, such that no further antibiotic therapy (IV or oral) or surgical or drainage procedure is required for the treatment of the cIAI. |
| Partial improvement (only at the EOIV Visit[2] for participants who switch to step-down therapy) | Partial resolution of signs and symptoms of the cIAI such that no further IV antibiotic therapy is required for the treatment of the cIAI; however, additional oral step-down therapy is required. |
| Failure | Any of the following is considered a clinical outcome of failure:<br>• Requirement of antibiotic therapy beyond the protocol-defined treatment duration of 14 days<br>• Persisting or recurrent infection within the abdomen requiring additional intervention, including nonstudy antibiotics or repeat surgical intervention.<br>• Post-surgical wound infection with signs of local infection, such as purulent exudate, erythema, or warmth that requires additional antimicrobial therapy and/or nonroutine wound care.<br>• Death related to IAI |
| Indeterminate | Trial data are not available for evaluation of efficacy for any reason, including death during the trial period unrelated to the cIAI or extenuating circumstances, which preclude classification as cure, partial improvement, or failure (e.g., participant is lost to follow-up). |
| **Microbiological Outcome[3]** | **Definition** |
| Eradication[4] | Absence of the baseline pathogen(s) in a postbaseline specimen appropriately obtained from the original site of infection. |
| Presumed Eradication[4] | Absence of material to culture in a participant who was assessed as having partial improvement, or clinical cure. |
| Persistence | Presence of the baseline pathogen(s) in an appropriately obtained postbaseline specimen from the site of infection or surgical wound.<br>NOTE: Cultures from indwelling drains were not considered appropriate. |
| Presumed Persistence | Absence of material to culture in a participant who was assessed as a clinical failure. |
| Persistence acquiring resistance | Presence of baseline pathogen(s) in an appropriately obtained postbaseline specimen where the baseline pathogen(s) was susceptible to study treatment pretreatment and is resistant to study treatment post-treatment. |
| Indeterminate | • Baseline culture either not obtained or has no growth.<br>• Postbaseline culture was not obtained and clinical assessment was not possible. |

| | |
|---|---|
| | • Any other circumstance that makes it impossible to define the microbiological response (e.g., participant lost to follow-up). |
| **Emergent Infection Outcome** | **Definition** |
| Superinfection | Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriately obtained postbaseline specimen in a subject while on study treatment. |
| New infection | Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriately obtained postbaseline specimen in a subject after administration of the last dose of study treatment and through the TOC visit. |

**Source: Applicant Table from Section 9.5 of CSR**
1- Clinical success rate was defined at the EOT and TOC visits as the proportion of participants in the analysis population who had a clinical response of "cure."
2- The clinical success rate at the EOIV visit was defined as the proportion of participants in the analysis population who had a clinical response of "cure" or "partial improvement." This definition included "partial improvement" to accommodate those with partial improvement switched to oral step-down therapy at this time point. For participants who received IV study treatment only (without optional oral step-down therapy), a separate assessment was not performed at the EOT Visit; the EOIV visit served as the EOT Visit.
3- The per-pathogen microbiological outcome was determined for each baseline infecting pathogen isolated by the Applicant.
4- Eradication or presumed eradication was considered favorable microbiological responses. In order for the participant to have a favorable overall microbiological response (i.e., eradication or presumed eradication), it was required that each baseline pathogen have a favorable microbiological outcome.

**Reviewer Comments:** *This review primarily considers the mMITT population for efficacy analyses. Analyses in the CE and ME populations can involve biases associated with post-baseline exclusions which may be related to the treatment received.*

**Statistical Analysis Plan**

Analysis Populations

- MITT population: All Randomized Participants who received any amount of study treatment. Participants were included in the IV study treatment group to which they were randomized.
- mMITT Population: subset of MITT participants who had at least 1 pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment.
- CE population: subset of MITT participants who adhered to study procedures and had a clinical outcome at the visit of interest. Participants with an indeterminate clinical outcome were excluded from the CE population.
- ME population: subset of participants in the CE population who had at least 1 pathogen identified from the baseline intra-abdominal culture regardless of susceptibility to treatment.

**Reviewer Comments:** *We generally recommend that the mMITT population include only treated subjects with a pathogen identified from the baseline intra-abdominal culture that is susceptible*

*to both study treatments which would allow for more appropriate comparisons. However, among participants included in the mMITT population of Study P035, all baseline gram-negative qualifying pathogens were susceptible to both C/T and MERO [90/90 (100%) susceptible to C/T and 89/89 (100%) susceptible to MERO].*

Methodology

To address the primary safety objective, Tier 2 endpoints were included. These were adverse events (AEs) of elevated laboratory values; the percentage of participants with any AE, serious adverse event (SAE), any study treatment-related AE, the percentage of participants discontinuing study medication due to an AE. AEs (specific preferred terms), system organ classes, or values outside the local laboratory's reference range with frequency of ≥ 2 participants in the comparator group (≥ 6 participants in the experimental group due to 3:1 randomization) which was the minimum number of participants to detect any differences between the groups. The 95% confidence intervals (CIs) are provided for between-treatment differences in the percentage of participants with events; these analyses were performed using the unstratified Miettinen and Nurminen (M&N) method (1985), an unconditional, asymptotic method.

To address the secondary objectives, a 2-sided 95% CI based on the M&N method and stratified by age group was provided to evaluate: (1) the treatment differences for clinical success at the EOT and TOC visits and (2) per-participant microbiological eradication at the EOT and TOC visits.

**Protocol Amendments**

The protocol amendments reflect the Applicant's prior submissions regarding changes to the protocols (SDN 336, 337 and 340) under IND 104490.

On May 1, 2020, the Applicant submitted a request for Agency agreement regarding proposed amendments to these PMR study protocols (SDN 336). The modifications were designed to expedite enrollment and completion of the pediatric studies. The proposed update included:

- Removal of the requirement that at least 4 subjects be enrolled in each study for Group 4 (3 months to <2 years) and Group 5 (birth to <3 months)

On May 5, 2020, the Division sent an IR requesting the Applicant's rationale on why PK (b) (4) As an alternative option, the Division recommended that the Applicant consider enrolling a minimum of 3 subjects in each group.

On May 12, 2020, the Applicant submitted a response (SDN 337) outlining the proposed approach for extrapolating the potential effect of age on ceftolozane and tazobactam PK in cIAI patients <2 years of age (group 4 and group 5) using a population PK modeling approach. The Division sent a correspondence on May 14, 2020, accepting the Applicant's proposal of updating the Group 4 and Group 5 enrollment targets.

On June 19, 2020, the Applicant submitted a proposal to end enrollment early in PN034 and PN035, with the currently enrolled combined total number of 222 subjects (representing a decrease from target overall minimum enrollment of 240 subjects), which would also reflect a decrease in the combined target minimum enrollment for Age Groups 3 (from 72 to 57 subjects) and 5 (from 24 to 21 subjects).

**Reviewer Comment:** *The amended protocol PN 035-03 was considered to be acceptable.*

### 8.1.4. Study Results of P035

**Compliance with Good Clinical Practices**

Per the Applicant, all trials were undertaken in accordance with standard operating procedures at the time of clinical conduct, which complied with the principles of Good Clinical Practice. All trials were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and its amendments in force at the time of the trial. All trials were approved by Ethics Committees or Institutional Review Boards and Competent authorities. Informed consent was obtained for all subjects.

**Financial Disclosure**

The Applicant submitted the required Financial Disclosure information. See section 15.1 for further information.

**Patient Disposition**

Patient disposition is described in **Table 8-19** and **Table 8-20**. In the C/T and MERO arms respectively, 94.4% and 87.0% of all randomized participants completed the study, 98.6% and 91.3% of participants received study treatment and qualified for the MITT population, and 88.7% and 82.6% of participants qualified for inclusion into the mMITT population. There were no major imbalances noted with respect to study completion rates and the percentage of participants who were clinically and microbiologically evaluable at the EOIV, EOT and TOC visits was generally similar between the study arms.

**Table 8-19: Patient Disposition (All Randomized Population, Study P035)**

| | **C/T+MTZ** | **MERO** |
|---|---|---|
| Patients in population | 71 (100%) | 23 (100%) |
| Completed study | 67 (94.4%) | 20 (87.0%) |
| Discontinued | 4 (5.6%) | 3 (13.0%) |
| Lost to Follow-up | 2 (2.8%) | 1 (4.3%) |
| Randomized in error | 0 | 1 (4.3%) |

| | | |
|---|---|---|
| Did not meet criteria after randomization and not dosed | 0 | 1 (4.3%) |
| Dispensing error | 1 (1.4%) | 0 |
| Withdrawal by Parent/Guardian | 1 (1.4%) | 0 |

**Source: Partially Adapted from CSR Table 14.1-2**

**Table 8-20: Patient Disposition by Defined Analysis Populations (All Randomized, P035)**

| **Population** | **C/T+MTZ** | **MERO** |
|---|---|---|
| All Randomized | 71 (100%) | 23 (100%) |
| All Participants as Treated (APaT) | 70 (98.6%) | 21 (91.3%) |
| Modified Intent-to-Treat (MITT) | 70 (98.6%) | 21 (91.3%) |
| Microbiological Modified Intent-to-Treat (mMITT) | 63 (88.7%) | 19 (82.6%) |
| Clinically Evaluable at EOIV | 61 (85.9%) | 20 (87.0%) |
| Clinically Evaluable at EOT | 59 (83.1%) | 19 (82.6%) |
| Clinically Evaluable at TOC | 58 (81.7%) | 19 (82.6%) |
| Microbiologically Evaluable at EOIV | 56 (78.9%) | 18 (78.3%) |
| Microbiologically Evaluable at EOT | 54 (76.1%) | 17 (73.9%) |
| Microbiologically Evaluable at TOC | 53 (74.6%) | 17 (73.9%) |

**Source: Partially Adapted from CSR Table 14.1-7**

**Protocol Violations/Deviations**

**Table 8-21** shows the important protocol violations occurring in the C/T+MTZ and MERO study arms in the All Participants As Treated (APaT) population of Study P035. Protocol deviations were similar overall in the C/T+MTZ and MERO study arms, 22 (31.4%) and 7 (33.3%), respectively, with deviations relating to inclusion/exclusion criteria higher in the C/T+MTZ arm, 8 (11.4%) and 0 (0.0%), and deviations relating to study intervention higher in the MERO study arm, 8 (11.4%) and 5 (23.8%). Reasons for the treatment imbalances in these categories of deviations are unclear.

**Table 8-21: Important Protocol Deviations (APaT Population, Study P035)**

| | **C/T+MTZ** N=70 | **MERO** N=21 |
|---|---|---|
| **One or more important protocol deviations** | 22 (31.4) | 7 (33.3) |

| | | |
|---|---|---|
| **Inclusion/exclusion Criteria**<br>Did not meet inclusion criteria 2, 4, 7, 8 or exclusion criteria 3, 4, 6-14 as defined in the protocol | 8 (11.4) | 0 |
| **Informed Consent**<br>No documented inform consent as required per age group | 1 (1.4) | 0 |
| **Prohibited Medications**<br>Received ≥ 1 dose of gram negative systemic antibiotics (except for 1 dose of prophylactive antibiotics) | 1 (1.4) | 0 |
| **Safety Reporting** | 3 (4.3) | 0 |
| Safety Event not reported per timelines in protocol | 1 (1.4) | 0 |
| Missed 1 or more scheduled safety adverse event assessments | 2 (2.9) | 0 |
| **Study Intervention** | 8 (11.4) | 5 (23.8) |
| Missed 2 or more consecutive doses of IV study medication | 0 | 1 (4.8) |
| Received <3 days or >15 days of study therapy (IV + oral combined) | 1 (1.4) | 0 |
| Received <80 or >120% of individual dose | 1 (1.4) | 0 |
| Was administered improperly stored study medication that was deemed unacceptable for use | 3 (4.3) | 3 (14.3) |
| Dispensed incorrect medication or potential cross-treatment | 1 (1.4) | 0 |
| Study drug infused over >30min or >90 min | 2 (2.9) | 2 (9.5) |
| **Trial Procedures** | 7 (10.0) | 3 (14.3) |
| EOIV, EOT, TOC, LFU, or oral safety assessment (when applicable) was 3 or more days outside of window | 4 (5.7) | 1 (4.8) |
| Missed 2 or more consecutive full sets of vital assessments | 2 (2.9) | 0 |
| Missed 2 or more scheduled safety blood draws | 1 (1.4) | 1 (4.8) |
| Missed scheduled EOIV, EOT or TOC clinical outcome assessment or assessment not done | 3 (4.3) | 1 (4.8) |

**Source: Partially Adapted from CSR Table 14.1-3**
Note: Every participant is counted a single time for each applicable row and column.

**Demographic and Baseline Characteristics**

**Table 8-22** shows the demographic and baseline characteristics for participants included in the modified intent-to-treat (MITT) population of Study P035. Given the high degree of variability that would be expected with only 21 patients in the meropenem arm, baseline characteristics were considered to be mostly balanced between the treatment arms with the exception of sex, where a substantially larger percentage of male patients were included in the C/T+MTZ arm versus the MERO arm, 47 (67.1%) versus 6 (28.6%), respectively.

**Table 8-22: Demographic and Baseline characteristics (MITT, P035)**

| Demographic Parameters | **C/T+MTZ** N=70 n (%) | **MERO** N=21 n (%) |
|---|---|---|
| **Sex** | | |
| Male | 47 (67.1) | 6 (28.6) |
| Female | 23 (32.9) | 15 (71.4) |
| **Age Group** | | |
| 12 to 18 years | 16 (22.9) | 5 (23.8) |
| 6 to <12 years | 30 (42.9) | 9 (42.9) |
| 2 to <6 years | 22 (31.4) | 7 (33.3) |
| 3 months to <2 years | 1( 1.4) | 0 |
| Birth to < 3 months | 1 (1.4) | 0 |
| **Age** | | |
| Mean years (SD) | 8.6 (4.4) | 8.5 (3.7) |
| Median (years) | 8.2 | 8.5 |
| Min, max (years) | 0.9, 17.6 | 3.4, 13.6 |
| **Race** | | |
| Asian | 3 (4.3) | 2 (9.5) |
| Black or African American | 5 (7.1) | 0 |
| Multiple | 1 (1.4) | 0 |
| White | 61 (87.1) | 19 (90.5) |
| **Ethnicity** | | |
| Hispanic or Latino | 18 (25.7) | 6 (28.6) |
| Not Hispanic or Latino | 49 (70.0) | 15 (71.4) |
| Not reported | 1 (1.4) | 0 |
| Unknown | 2 (2.9) | 0 |
| **Region** | | |
| North America | 26 (37.1) | 7 (33.3) |
| Europe | 37 (52.9) | 13 (61.9) |
| South America | 1 (1.4) | 0 |
| Africa | 4 (5.7) | 0 |
| Asia/Pacific | 2 (2.9) | 1 (4.8) |

**Source: Partially Adapted from CSR Table 14.1-8**

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

**Table 8-23** compares other baseline characteristics between treatments in the MITT population. Given the limited number of patients in the MERO arm, some imbalances were observed. For example, compared to the MERO arm, the C/T+MTZ arm included a smaller percentage of patients with eGFR at or above 80 (87.1% versus 100%), with multiple baseline pathogens (54.3% versus 66.7%) and with complicated appendicitis (91.4% versus 100%),

**Table 8-23: Other Baseline characteristics (MITT, P035)**

| Baseline Parameters | **C/T+MTZ** N=70 n (%) | **MERO** N=21 n (%) |
|---|---|---|
| **Baseline Diagnosis** | | |
| Complicated Appendicitis | 64 (91.4) | 21 (100) |
| Other complicated IAI | 6 (8.6) | 0 |
| **Bacteremia at Baseline** | | |
| Yes | 2 (2.9) | 0 |
| No | 68 (97.1) | 21 (100) |
| **Height (cm)** | | |
| Mean (SD) | 129.5 (26.8) | 129.6 (23.6) |
| Median (range) | 130.2 (54 to 180) | 132 (87 to 160) |
| **Weight (kg)** | | |
| Mean (SD) | 32.8 (19.2) | 31.2 (13.9) |
| Median (range) | 27.7 (3.1 to 90.0) | 30.5 (11 to 61.1) |
| **Baseline eGFR** | | |
| eGFR ≥ 80 | 61 (87.1) | 21 (100) |
| eGFR ≥ 50 to < 80 | 8 (11.4) | 0 |
| eGFR ≥ 30 to < 50 | 1 (1.4) | 0 |
| **Failure of Prior Therapy** | | |
| Yes | 1 (1.4) | 0 |
| No | 69 (98.6) | 21 (100) |
| **Prior Antibiotic Use** | | |
| Yes | 67 (95.7) | 21 (100) |
| No | 3 (4.3) | 0 |
| **Number of Baseline Pathogens** | | |
| Polymicrobial | 38 (54.3) | 14 (66.7) |
| Monomicrobial | 26 (37.1) | 5 (23.8) |
| Missing | 6 (8.6) | 2 (9.5) |

**Source: Partially Adapted from CSR Table 14.1-8**

**Treatment Compliance and Concomitant Medications**

**Table 8-24** shows the overall treatment compliance for the C/T+MTZ and MERO study arms in the APaT population of Study P035. Compliance was generally similar between the study arms with nearly all participants having at least 80% compliance. Only one participant in the C/T+MTZ arm had less than 80% compliance (i.e., 50.0% compliance). The percentages of participants with > 80% to 100% compliance and > 100% compliance were similar between treatment arms.

**Table 8-24: Treatment Compliance (APaT, P035)**

| | **C/T+MTZ**<br>N=70<br>n (%) | **MERO**<br>N=21<br>n (%) |
|---|---|---|
| **Overall Treatment Compliance** | | |
| ≤ 80% | 1 (1.4) | 0 (0.0) |
| > 80% to ≤ 100% | 44 (62.9) | 14 (66.7) |
| > 100% | 25 (35.7) | 7 (33.3) |
| **Summary Statistics for overall treatment compliance** | | |
| Mean (SD) | 98.9 (6.5) | 99.7 (1.1) |
| Median (range) | 100.0 (50.0 to 104.3) | 100.0 (98.1 to 102.4) |

**Source: Partially Adapted from CSR Table 14.1-37**

**Table 8-25** shows the use of concomitant antibacterials in the MITT population of Study P035. The percentage of patients using one or more concomitant antibacterials through the TOC visit was slightly greater in the C/T arm versus the MERO arm, 17 (24.3%) versus 4 (19.0%). The most common antibacterials used were amoxicillin, amoxicillin with clavulanate potassium, and metronidazole.

**Table 8-25: Participants with Concomitant Antibacterial Use through TOC Visit (MITT, P035)**

| | **C/T+MTZ**<br>N=70<br>n (%) | **MERO**<br>N=21<br>n (%) |
|---|---|---|
| **Concomitant antibacterials for systemic use** | 17 (24.3) | 4 (19.0) |
| Amoxicillin | 3 (4.3) | 1 (4.8) |
| Amoxicillin; Clavulanate Potassium | 3 (4.3) | 1 (4.8) |
| Ceftriaxone | 2 (2.9) | 1 (4.8) |
| Ciprofloxacin | 2 (2.9) | 0 |
| Clavulanic Acid | 2 (2.9) | 0 |
| Gentamicin | 1 (1.4) | 1 (1.4) |
| Meropenem | 3 (4.3) | 0 |
| Metronidazole | 4 (5.7) | 0 |

| | | |
|---|---|---|
| Piperacillin Sodium, Tazobactam Sodium | 2 (2.9) | 1 (4.8) |
| Vancomycin | 2 (2.8) | 0 |

**Source: Partially Adapted from CSR Table 14.1-35**
Note: Only antibacterials used by two or more participants are included above

**Efficacy Results – Secondary Efficacy Endpoints**

The primary endpoints of Study P035 were related to assessment of AEs, laboratory data, and vital signs in the APaT population. Efficacy endpoints in Study P035, specified as secondary, were intended to provide point estimates of the efficacy of each treatment regimen since the study was not powered for the formal hypothesis testing of between treatment group comparisons. These endpoints included clinical success rates and per-patient microbiological success rates at EOT and TOC visits in the MITT, mMITT, CE and ME populations. Note that this review mainly considers the MITT and mMITT populations.

**Table 8-26** shows the clinical response rates at the EOT and TOC visits for participants included in the MITT and mMITT populations of Study P035. Clinical success rates were defined as the proportion of participants in the analysis population with a response of "cure", as previously defined in **Table 8-18**.

Success rates at EOT and TOC were high in both study arms but were numerically lower in the C/T+MTZ arm compared to the MERO arm. In the MITT population, clinical success rates at the TOC visit for the C/T+MTZ arm versus the MERO arm were 56/70 (80.0%) versus 21/21 (100%); an adjusted difference of -19.1% (95% CI: -30.2, -2.9). In the mMITT population, clinical success rates at the TOC visit were 53/63 (84.1%) versus 19/19 (100%); an adjusted difference of -16.3% (95% CI: -27.6, 1.4).

**Table 8-26: Clinical Response at EOT and TOC Visits (MITT/mMITT, P035)**

| | **C/T+MTZ** n (%) | **MERO** n (%) | **Difference (95% CI)** (C/T+MTZ – MERO) (%) |
|---|---|---|---|
| **MITT Population** | | | |
| **EOT Visit** | N=70 | N=21 | |
| Success | 56 (80.0) | 20 (95.1) | -14.3 (-26.7, 4.9) |
| Failure | 14 (20.0) | 1 (4.8) | |
| Observed Failure | 8 (11.4) | 0 | |
| Observed Indeterminate | 3 (4.3) | 0 | |
| Imputed Indeterminate | 3 (4.3) | 1 (4.8) | |
| **TOC Visit** | N=70 | N=21 | |
| Success | 56 (80.0) | 21 (100) | -19.1 (-30.2, -2.9) |
| Failure | 14 (20.0) | 0 | |
| Observed Failure | 8 (11.4) | 0 | |
| Observed Indeterminate | 3 (4.3) | 0 | |
| Imputed Indeterminate | 3 (4.3) | 0 | |
| | | | |

| **mMITT Population** | N=63 | N=19 | |
|---|---|---|---|
| **EOT Visit** | | | |
| Success | 53 (84.1) | 18 (94.7) | -11.2 (-23.7, 9.6) |
| Failure | 10 (15.9) | 1 (5.3) | |
| Observed Failure | 6 (9.5) | 0 | |
| Observed Indeterminate | 1 (1.6) | 0 | |
| Imputed Indeterminate | 3 (4.8) | 1 (5.3) | |
| **TOC Visit** | | | |
| Success | 53 (84.1) | 19 (100) | -16.3 (-27.6, 1.4) |
| Failure | 10 (15.9) | 0 | |
| Observed Failure | 6 (9.5) | 0 | |
| Observed Indeterminate | 1 (1.6) | 0 | |
| Imputed Indeterminate | 3 (4.8) | 0 | |

**Source: Partially Adapted from CSR Table 11-1, 11-2, 14.2-5**
The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights.

**Table 8-27** shows the per-participant microbiological response rates at the EOT and TOC visits for participants included in the mMITT population of Study P035. Eradiation rates at EOT and TOC were high in both study arms but were numerically lower in the C/T+MTZ arm compared to the MERO arm.

At the EOT visit, eradication rates in the C/T+MTZ arm versus the MERO arm were 53/63 (84.1%) versus 18/19 (94.7%), an adjusted difference of -11.2% (95% CI: -23.7, 9.6). At the TOC visit, eradication rates were 53/63 (84.1%) versus 19/19 (100%), an adjusted difference of -16.3% (95% CI: -27.6, 1.4). Of the 10 participants with microbiological failure at TOC, 6 (9.5%) had presumed persistence and 4 (6.3%) were indeterminate. Therefore, the difference in presumed persistence rates at TOC was slightly less pronounced than the differences in presumed eradication rates at TOC.

**Reviewer Comments:** *As most participants in P035 did not have postbaseline intra-abdominal cultures, the majority of microbiologic outcomes were based on presumed eradication (i.e., clinical success in participants who did not have follow-up postbaseline intra-abdominal cultures) rather than documented eradication of the infecting organism.*

**Table 8-27: Per-Participant Microbiological Outcome at EOT and TOC Visits (mMITT, P035)**

| | **C/T+MTZ** n (%) | **MERO** n (%) | **Difference (95% CI)** (C/T+MTZ – MERO) (%) |
|---|---|---|---|
| **EOT Visit** | N=63 | N=19 | |
| Microbiological Success | 53 (84.1) | 18 (94.7) | -11.2 (-23.7, 9.6) |
| Presumed Eradication | 53 (84.1) | 18 (94.7) | |
| Microbiological Failure | 10 (15.9) | 1 (5.3) | |
| Presumed Persistence | 6 (9.5) | 0 | |

| | | | |
|---|---|---|---|
| Indeterminate | 4 (6.3) | 1 (5.3) | |
| **TOC Visit** | N=63 | N=19 | |
| Microbiological Success | 53 (84.1) | 19 (100) | -16.3 (-27.6, 1.4) |
| Presumed Eradication | 53 (84.1) | 19 (100) | |
| Microbiological Failure | 10 (15.9) | 0 | |
| Presumed Persistence | 6 (9.5) | 0 | |
| Indeterminate | 4 (6.3) | 0 | |

**Source: Partially Adapted from CSR Table 11-4**
The % difference is based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel (CMH) weights.

Clinical success rates and per-participant microbiological success (presumed eradication) rates by age group (i.e., between-treatment groups within each age group and across age groups) were generally consistent with the overall clinical success rates by treatment group. The per-participant microbiological success rates in the ME population were also generally consistent with those reported in the mMITT populations for both the TOC and EOT visits.

**Reviewer comments:** *The clinical response rates in the C/T+MTZ group were comparable to the clinical response in the pivotal Phase 3 cIAI study, which demonstrated the noninferiority of C/T+MTZ to MERO in adult participants with cIAI (C/T+MTZ: 83.0%; MERO 87.3%). Therefore, it is possible that the difference in clinical success between the C/T+MTZ group and the MERO group may have been driven in part by a high cure rate in the MERO group. Also, in Study P035, six of the 14 failures at the TOC visit in the C/T+MTZ group (MITT population) were based on indeterminate or missing clinical responses.*

**Data Quality and Integrity**

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

**Efficacy Results – Secondary and other relevant endpoints**

The secondary efficacy endpoints of clinical success in the MITT and mMITT populations and per-participant microbiological response in the mMITT population listed above were considered most relevant. Other exploratory endpoints of potential relevance included clinical response and per-participant microbiological response at the EOIV Visit and per-pathogen microbiological response at the TOC Visit. As shown in **Table 8-28**, treatment differences for these outcomes followed trends which were similar to those observed for these outcomes at the EOT and TOC visits.

**Table 8-28: Clinical Response and Per-Participant Microbiological Response at the EOIV Visit (mMITT/MITT, P035)**

| | **C/T+MTZ** n (%) | **MERO** n (%) | **Difference (95% CI)** (C/T+MTZ–MERO) (n%) |
|---|---|---|---|
| **Clinical Response at EOIV Visit (MITT)** | N=70 | N=21 | |
| Success | 61 (87.1) | 21 (100) | -11.8 (-21.8, 4.2) |
| Partial Improvement | 35 (50.0) | 12 (57.1) | |
| Cure | 26 (37.1) | 9 (42.9) | |
| Failure | 9 (12.9) | 0 | |
| Observed Failure | 5 (7.1) | 0 | |
| Observed Indeterminate | 3 (2.8) | 0 | |
| Imputed Indeterminate | 1 (1.4) | 0 | |
| **Clinical Response at EOIV Visit (mMITT)** | N=63 | N=19 | |
| Success | 57 (90.5) | 19 (100) | -10.1 (-20.2, 7.2) |
| Partial Improvement | 32 (50.8) | 11 (57.1) | |
| Cure | 25 (39.7) | 8 (42.9) | |
| Failure | 6 (9.5) | 0 | |
| Observed Failure | 4 (6.3) | 0 | |
| Observed Indeterminate | 1 (1.6) | 0 | |
| Imputed Indeterminate | 1 (1.6) | 0 | |
| **Per-Participant Microbiological Response at EOIV Visit (mMITT)** | N=63 | N=19 | |
| Microbiological Success | 57 (90.5) | 19 (100) | -10.1 (-20.2, 7.2) |
| Presumed Eradication | 57 (90.5) | 19 (100) | |
| Microbiological Failure | 6 (9.5) | 0 | |
| Persistence | 1 (1.6) | 0 | |
| Presumed Persistence | 4 (6.3) | 0 | |
| Indeterminate | 1 (1.6) | 0 | |

**Source: Partially Adapted from CSR Tables 14.2-21, 14.2-22 and 14.2-24**
The % difference is based on the Miettinen & Nurminen method stratified by age group CMH weights.

Other exploratory secondary endpoints included the per-pathogen microbiological response at the TOC Visit in the mMITT population shown in **Table 8-29**. From this table, a large percentage of participants are shown to have pathogens of the 'Enterobacterales' order, most commonly *Escherichia coli*. There were no clear trends regarding treatment differences in microbiological success for specific pathogens or pathogen groups. However, substantially lower success rates were observed for participants in the C/T+MTZ arm having a gram-positive pathogen, 14/19 (73.7) versus 10/10 (100) in the MERO arm. Note that comparisons in this table are limited by small numbers.

**Table 8-29: Per-Pathogen Microbiological Success at the TOC Visit (mMITT, P035)**

| | **C/T+MTZ** N=63 n/N (%) | **MERO** N=19 n/N (%) |
|---|---|---|
| | | |
| **Aerobic Gram-negative** | 48/56 (85.7) | 18/18 (100) |
| **Enterobacterales** | 40/47 (85.1) | 13/13 (100) |
| *Escherichia coli* | 40/47 (85.1) | 13/13 (100) |
| *Klebsiella pneumoniae* | 3/4 (75.0) | 0/0 |
| *Pseudomonas aeruginosa* | 17/19 (89.5) | 6/6 (100) |
| **Aerobic Gram-positive** | 14/19 (73.7) | 10/10 (100) |
| *Streptococcus anginosus* | 7/9 (77.8) | 3/3 (100) |
| *Streptococcus constellatus* | 7/9 (77.8) | 3/3 (100) |
| **Anaerobic Gram-negative** | 13/16 (81.3) | 5/5 (100) |
| *Bacteroides fragilis* | 10/13 (76.9) | 4/4 (100) |
| *Bacteroides thetaiotaomicron* | 4/4 (100) | 2/2 (100) |
| **Anaerobic Gram-Positive** | 6/8 (75.0) | 2/2 (100) |

**Source: Partially Adapted from CSR Tables 14.2-26**
N= Number of participants in specific population of pathogen or pathogen category
n=Number of participants in specific category
Participants with missing/indeterminate microbiological outcome counted as having 'persistence'

**Durability of Response**

Efficacy data beyond the TOC visit was not collected. There were no concerns related to the durability of the response through the TOC visit. Treatment differences in clinical response rates between the C/T+MTZ and MERO arms did not indicate an unfavorable trend across the EOIV, EOT and TOC visits.

**Persistence of Effect**

The persistence of effect of C/T is not anticipated to be of long duration, due to its rapid elimination (approximately 2 to 3 hours for ceftolozane and 1 hour for tazobactam).

**Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

There were no additional secondary or exploratory COA (PRO) endpoints defined.

**Additional Analyses Conducted on the Individual Trial**

Additional analyses conducted on Study P035 included subgroup analyses of clinical cure rates at the TOC visit for various subgroup categories in the MITT population. **Table 8-30** shows the proportions of subjects who were clinical cures at TOC who fell into these subgroups. There were no notable findings identified when considering clinical cure rates in these subgroups.

Note that comparisons between treatment arms by subgroup were limited due to the small numbers of participants in the MERO arm.

**Table 8-30: Subgroup Analyses of Participants with Clinical Cure at TOC Visit (MITT, P035)**

| | **C/T+MTZ**<br>N=70<br>n/N (%) | **MERO**<br>N=21<br>n/N (%) |
|---|---|---|
| **Age Group** | | |
| 12 to <18 years | 15/16 (93.8) | 5/5 (100) |
| 6 to <12 years | 23/30 (76.7) | 9/9 (100) |
| 2 to < 6 years | 17/22 (77.3) | 7/7 (100) |
| 3 months to < 2 years | 0/1 (0) | 0/0 |
| 0 to < 3 months | 1/1 (100) | 0/0 |
| **Sex** | | |
| Male | 39/47 (83.0) | 6/6 (100) |
| Female | 17/23 (73.9) | 15/15 (100) |
| **Region** | | |
| North America | 20/26 (76.9) | 7/7 (100) |
| Europe | 33/37 (89.2) | 13/13 (100) |
| Other | 3/7 (42.9) | 1/1 (100) |
| **Duration of IV Study Treatment** | | |
| < 7 days | 33/43 (76.7) | 16/16 (100) |
| ≥ 7 days | 23/27(85.2) | 5/5 (100) |
| **Number of Abscesses** | | |
| Single | 16/20 (80.0) | 5/5 (100) |
| Multiple | 40/50 (80.0) | 16/16 (100) |
| **Peritonitis Type** | | |
| Local | 13/18 (72.2) | 9/9 (100) |
| Diffuse | 24/27 (88.9) | 6/6 (100) |
| Missing | 19/25 (76.0) | 6/6 (100) |
| **Prior Antibiotic Use** | | |
| Yes | 53/67 (79.1) | 21/21 (100) |
| No | 3/3 (100) | 0/0 |
| **Site of Infection** | | |
| Appendix | 52/64 (81.3) | 21/21 (100) |
| Nonappendix | 4/6 (66.7) | 0/0 |
| **Bacteremia at Baseline** | | |
| Yes | 2/2 (100) | 0/0 |
| No | 54/68 (79.2) | 21/21 (100) |
| **Number of Baseline Pathogens** | | |
| Polymicrobial | 31/38 (81.6) | 14/14 (100) |
| Monomicrobial | 22/26 (84.6) | 5/5 (100) |
| Missing | 3/6 (50.0) | 2/2 (100) |

**Source: Partially Adapted from CSR Tables 14.2-4 and 14.2-13**

## Integrated Review of Effectiveness

### 8.1.5. Assessment of Efficacy Across Trials

Due to differences in types of infection and study design factors, the efficacy of ZERBAXA was not assessed across the P034 and P035 trials.

However, the efficacy of ZERBAXA was compared between Study P034 and the adult Study -04&05 for cUTI (**Table 8-31**) and between Study P035 and the adult Study -08&09 for cIAI (**Table 8-32**). Study -04&05 and Study -08&09 were submitted in the original NDA submitted on April 21, 2014. Study -04&05 was a phase 3, multicenter, randomized, double-blind, placebo dummy, non-inferiority trial of C/T (1.5 g every 8 hours) administered as an IV infusion versus levofloxacin (LEVO) (750 mg daily) in the treatment of adults with cUTI. Study -08&09 was a phase 3, multicenter, randomized, double-blind, placebo dummy, non-inferiority trial of C/T (1.5 g every 8 hours) plus MTZ (500 mg every 8 hours) versus MERO (1 g every 8 hours) administered as an IV infusion in the treatment of adults with cIAI requiring surgical intervention.

**Table 8-31: Clinical and Microbiological Response at TOC Visit (cUTI Studies P034 and -04&05)**

| **Study P034 (mMITT[1])** | **C/T** n (%) | **MERO** n (%) | **Difference (95% CI)** (C/T – MERO) (%) |
|---|---|---|---|
| **Clinical Response at TOC Visit[2]** | N=71 | N=24 | |
| Success[3] | 63 (88.7) | 23 (95.8) | -7.3 (-18.0, 10.1) |
| Failure | 4 (5.6) | 1 (4.2) | |
| Indeterminate | 4 (5.6) | 0 | |
| **Microbiological Response at TOC Visit[2]** | N=71 | N=24 | |
| Success[4] | 60 (84.5) | 21 (87.5) | -3.0 (-17.1, 17.4) |
| Failure | 4 (5.6) | 3 (12.5) | |
| Indeterminate | 7 (9.9) | 0 | |
| | | | |
| **Study -04&05 (mMITT[1])** | **C/T** n (%) | **LEVO** n (%) | **Difference (95% CI)** (C/T – LEVO) (%) |
| **Clinical Response at TOC Visit[2]** | N=398 | N=402 | |
| Success[3] | 366 (92.0) | 356 (88.6) | 3.4 (-0.7, 7.6) |
| Failure | 20( 5.0) | 35 (8.7) | |
| Indeterminate | 12 (3.0) | 11 (2.7) | |
| **Microbiological Response at TOC Visit[2]** | N=398 | N=402 | |
| Success[4] | 320 (80.4) | 290 (72.1) | 8.3 (2.4, 14.1) |
| Failure | 51 (12.8) | 85 (21.1) | |
| Non-evaluable | 12 (6.8) | 27 (6.7) | |

**Source: Partially Adapted from CSR Tables 11-1 and 11-2, and Table 11 of Statistical Review of original NDA submission of April 21, 2014**

1- In both studies, the mMITT population included randomized participants receiving any amount of study drug with at least one pathogen identified from the baseline culture, regardless of susceptibility to study treatment.
2- In Study -04&05, TOC Visit was 7 days after last dose. In Study P035, it was 5-9 days after last dose
3- In both studies, clinical success required complete resolution or improvement in signs and symptoms (or return to preinfection signs and symptoms), such that no additional antibacterial therapy was required for the treatment of the cUTI.
4- In both studies, microbiological success required eradication or presumed eradication of the baseline pathogen

**Reviewer Comments:** *Although these studies had major differences in their respective designs (e.g., objectives, dosing regimen, entry criteria, sample size, and hypothesis testing) both the clinical and microbiological response rates in the C/T arm at the TOC visit were comparable between studies. Efficacy data obtained from Study P034 will provide additional evidence for efficacy in treatment of pediatric patients with cUTI.*

**Table 8-32: Clinical Response at TOC Visit in cIAI Studies (Studies P035 and -08&09)**

| | **C/T+MTZ** n (%) | **MERO** n (%) | **Difference (95% CI)** (C/T+MTZ – MERO) (%) |
|---|---|---|---|
| **Study P035 (MITT[1])** | N=70 | N=21 | |
| **TOC Visit[3]** | | | |
| Success[4] | 56 (80.0) | 21 (100) | -19.1 (-30.2, -2.9) |
| Failure | 8 (11.4) | 0 | |
| Indeterminate | 6 (8.6) | 0 | |
| | | | |
| **Study P035 (mMITT[2])** | N=63 | N=19 | |
| **TOC Visit[3]** | | | |
| Success[4] | 53 (84.1) | 19 (100) | -16.3 (-27.6, 1.4) |
| Failure | 6 (9.5) | 0 | |
| Indeterminate | 4 (6.4) | 0 | |
| | | | |
| **Study -08&09 (MITT[2])** | N=389 | N=417 | |
| **TOC Visit[3]** | | | |
| Success[4] | 323 (83.0) | 364 (87.3) | -4.3 (-9.2, 0.7) |
| Failure | 32 (8.2) | 34 (8.2) | |
| Indeterminate | 34 (8.7) | 19 (4.6) | |

**Source: Partially Adapted from CSR Tables 11-1 and 11-4, and Table 6 of Statistical Review of original NDA submission of April 21, 2014**
1- MITT (P035) included randomized participants receiving any amount of treatment,
2- mMITT (P035) and MITT (-08&09) populations both included randomized participants having at least one pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment. mMITT (P035) also required participants to receive study treatment.
3- In Study -08&09, TOC Visit was 24-32 days after last dose. In Study P035, it was 7-14 days after last dose
4- In both studies, clinical success required complete resolution or improvement in signs and symptoms of the cIAI (or return to preinfection signs and symptoms if Study P035), such that no additional antibacterial therapy or surgical or drainage procedure was required for the treatment of the cIAI.

**Reviewer Comments:** *Although Studies P035 and -08&09 had major differences in their respective designs, point estimates for the clinical success rates at TOC in the CT+MTZ arm were similar between studies. This suggests that the less favorable treatment difference observed in Study P035 may have largely been due to the higher than expected point estimate for the clinical success rate at TOC in the MERO arm (i.e., a 100% success rate). Efficacy data obtained from Study P035 will provide additional evidence for efficacy in treatment of pediatric patients with cIAI.*

#### 8.1.6. Integrated Assessment of Effectiveness

Due to differences in types of infection and study design factors, an integrated assessment of effectiveness across the P034 and P035 trials was not considered. Note that since the course of disease and the effects of the drug are sufficiently similar in adults and pediatric patients, efficacy in pediatric patients was mainly extrapolated from adults (see sections 6.1 and 15.2.1.2). Additional evidence is obtained from the two phase 2 pediatric safety, efficacy, and PK studies (P034 and P035) that evaluated the proposed pediatric C/T dosage.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The safety of ZERBAXA in adults was previously reviewed in the original NDA for the treatment of cIAI and cUTI. The current safety review primarily focuses on the safety findings from the two double-blinded, randomized, multicenter active-controlled studies of pediatric patients from birth to less than 18 years of age. Study P035 compared C/T + MTZ to MERO for treatment of cIAI. Study 034 compared C/T to MERO for treatment of cUTI.

Of note, the Applicant also conducted a phase 1 pediatric study, Study P010, which was a single-dose, non-comparative, open-label study aimed at evaluating the PK and safety; safety data from Study P010 were reviewed. However, given the limitation of the study design, only a summary of safety data from Study P010 is included in this review (see Section 8.2.8).

A summary of safety results from studies P035 (cIAI) and P034 (cUTI) is presented in Table 8-33 below.

**Table 8-33: Summary of Adverse Events in the All Participants as Treated Population, Pooled Phase 2 Pediatric Studies P035 (cIAI) and P034 (cUTI)**

| AE Category | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| | P035 (cIAI) | | P034 (cUTI) | | Total | |
| | C/T + MTZ | MERO | C/T | MERO | C/T ± MTZ | MERO |

| | (N=70) | (N=21) | (N=100) | (N=33) | (N=170) | (N=54) |
|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Any AE** | 56 (80) | 13 (62) | 59 (59) | 20 (61) | 115 (68) | 33 (61) |
| **Any AE with an outcome of death** | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Any SAE** | 8 (11) | 0 (0) | 3 (3) | 2 (6) | 11 (7) | 2 (4) |
| **Discontinuation due to AE** | 2 (3) | 0 (0) | 1 (1) | 0 (0) | 3 (2) | 0 (0) |
| **Discontinuation due to SAE** | 2 (3) | 0 (0) | 0 (0) | 0 (0) | 2 (1) | 0 (0) |
| **Any AE of severe intensity** | 5 (7) | 0 (0) | 5 (5) | 1 (3) | 10 (6) | 1 (2) |

Percentages are based on the total number of patients in the treatment group (N).
Source: Reviewer generated based on Page 23 of 2.7.4 Summary of Clinical Safety and page 177 of 5.3.5.3.3 Integrated Summary of Safety

### 8.2.2. Review of the Safety Database

**Overall Exposure**

In total, 70 pediatric patients were exposed to C/T + MTZ in the P035 (cIAI) study and 100 pediatric patients were exposed to C/T in the P034 (cUTI) study for a total of 170 patients. A total of 54 patients received the comparator drug, meropenem. There were more patients in the older age groups in the cIAI study, as demonstrated in Table 8-34 below. The median age of C/T + MTZ and MERO exposed patients in cIAI study was 8.2 and 8.5, respectively. The median age of C/T and MERO exposed patients in cUTI study was 3.9 and 3.1, respectively. The two studies were evaluated separately due to differences in the underlying conditions, demographics, and exposures of the patients. An additional 37 pediatric patients were exposed to C/T in a phase 1 PK study (P010). Table 8-35 provides information on the dosage regimens utilized in Study P010 based on age group.

**Table 8-34: Exposure to ZERBAXA by Age Group in Studies P035 (cIAI) and P034 (cUTI)**

| | Patients Exposed to C/T (N=170) | | |
|---|---|---|---|
| **Age Group** | **cIAI** | **cUTI** | **Total** |
| **Group 1 (12 to <18 years)** | 16 | 15 | 31 |

| | | | |
|---|---|---|---|
| **Group 2 (6 to <12 years)** | 30 | 24 | 54 |
| **Group 3 (2 to <6 years)** | 22 | 22 | 44 |
| **Group 4 (3 months to < 2 years)** | 1 | 24 | 25 |
| **Group 5 (Birth to <3 months )** | 1 | 15 | 16 |
| **Total** | 70 | 100 | 170 |

Source: Reviewer generated based on Table 10-1 of CSRs P034 and P035

**Table 8-35: Exposure to ZERBAXA by Age Group in Study P010 (PK)**

| Age Group | Patients Exposed to C/T (Dose) |
|---|---|
| Group 1 (N=6), 12 to <18 years | 6 (1.5 g C/T) |
| Group 2 (N=6), 7 to <12 years | 6 (18 mg/kg TOL/ 9 mg/kg TAZ) |
| Group 3 (N=6), 2 to <7 years | 3 (18 mg/kg TOL/ 9 mg/kg TAZ) |
| | 3 (30 mg/kg TOL/ 15 mg/kg TAZ) |
| Group 4 (N=6), ≥3 months to <2 years | 1 (18 mg/kg TOL/ 9 mg/kg TAZ) |
| | 5 (30 mg/kg TOL/ 15 mg/kg TAZ) |
| Group 5 (N=7), Birth (>32 weeks gestation, >7 days postnatal) to <3 months | 7 (20 mg/kg TOL/ 10 mg/kg TAZ) |
| Group 6 (N=6), Birth (≤32 weeks gestation, >7 days postnatal) to <3 months | 2 (12 mg/kg TOL/ 6 mg/kg TAZ) |
| | 4 (20 mg/kg TOL/ 10 mg/kg TAZ) |
| Total | 37 |

Source: Partially Adapted from CSR P010 Table 10-1

**Adequacy of the Safety Database**

The safety database was adequate in terms of the size and population in question. Safety evaluations included vital signs, ECGs, routine physical examination, and laboratory tests. Patients were monitored for adverse events including cephalosporin class effects. 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 23.1 used during the study.

**Categorization of Adverse Events**

The severity of the AEs were characterized as:

• Mild: awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)

• Moderate: discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)

• Severe: incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)

**Reviewer comments**: *The categorization of the severity of adverse events was adequate.*

**Routine Clinical Tests**

Routine chemistry (albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium, total bilirubin, direct bilirubin [only if total bilirubin is > upper limit of normal {ULN}], total protein, and BUN) and hematology (hematocrit, hemoglobin, platelets, leukocytes (total and differential), and direct Coombs' test) laboratory tests were obtained.

**Reviewer comments:** *The routine clinical tests were adequate.*

### 8.2.4. Safety Results

**Deaths**

There were no deaths reported in any of the studies.

**Serious Adverse Events (SAE)**

Among the 13 SAEs reported (P034: 3 ZERBAXA, 2 meropenem; P035: 8 ZERBAXA+MTZ, 0 meropenem), 4 occurred (P034: 1 meropenem, P035: 3 ZERBAXA+MTZ) while participants were receiving IV therapy. All SAEs resolved except for 1 (P034: 1 meropenem; hypertension), which resolved with sequelae.

**Reviewer comments:** *In study P034, 3 patients who received ZERBAXA developed SAEs which included pyelonephritis and upper respiratory tract infection. These SAEs are a progression of disease or another infection unrelated to ZERBAXA use. In study P035, 8 patients who received ZERBAXA developed SAEs. These patients were in age groups 2 and 3. Progression of disease including abdominal sepsis and intra-abdominal fluid collection were reported in 2 patients. Other infections such as pneumonia, lower respiratory tract infection, and bacterial arthritis occurred in 3 patients. One patient developed leukocytosis which resolved in one day. One patient developed constipation of moderate intensity 24 days after the last dose of ZERBAXA. One patient developed fecaloma of mild intensity that resolved in 2 days. Overall, there were no specific SAEs that appeared to be related to ZERBAXA use.*

*One patient in Study P034 who received MERO developed an SAE of hypertension that resolved with sequelae. The patient was a male of 104 days of age (group 4), who was born with a congenital hypoplastic right kidney, developed exacerbation of hypertension while on the study treatment. The patient was found to have vesicouretheral reflux and right sided nephroureterectomy was performed. The patient was also found to have left renal artery stenosis and required anti-hypertensive treatment. The investigator assessed the SAE as not related to the study treatment. The reviewer agrees with the investigator's assessment.*

**Dropouts and/or Discontinuations Due to Adverse Effects**

In study P035 (cIAI), 2 patients developed SAEs and discontinued the study treatment. Both patients were receiving C/T + MTZ treatment. One patient was a female, 3 years of age (Group 3) who was diagnosed with complicated appendicitis and peritonitis. The patient developed pneumonia on Day 10 of treatment and the study treatment was discontinued. The other patient was a male, 2 years of age (Group 3) who was diagnosed with complicated appendicitis and diffuse peritonitis. On Day 3, he developed abdominal sepsis and pneumonia and the study treatment was discontinued. The patient also developed intestinal obstruction on Day 12. The SAEs resolved in both patients. There were no SAEs in the MERO group.

In study P034 (cUTI), 1 patient developed an AE of mild intensity but discontinued the study treatment. The patient was a female of 7 years of age (Group 2) receiving C/T who developed worsening of creatinine and decreased GFR to 43.3 mL/min/1.73 $m^2$ on Day 2. The study treatment was discontinued and the GFR recovered the next day. The study treatment was not resumed.

**Reviewer comments:** *The cases of discontinuation due to AEs appear to be attributable to disease progression rather than an adverse reaction to the study treatment.*

**Significant Adverse Events**

AEs of anaphylaxis, hypersensitivity, severe skin reaction, 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 reactions, or CDAD, were reported in studies P034 or P035. There was one AE of oliguria reported in the C/T+MTZ group in study P035 which was a non-serious, resolved, and the patient did not require discontinuation of study treatment. Also there was one case of worsening creatinine in the C/T group in study P034 which caused the participant to discontinue study treatment. A detailed description of this case is provided in the Dropouts and/or Discontinuations Due to Adverse Effects section. There was one AE of transfusion reaction reported in the C/T+MTZ group in study P035 which was a non-serious, resolved, and the patient did not discontinue study treatment. Patient was found to have seroconversion of Coombs' test.

Most AEs were mild to moderate in severity and comparable between both treatment groups. In study P034, 5 patients developed severe AEs in the C/T group. Severe neutropenia was noted

in 2 patients. Single cases of pyrexia, pyelonephritis, and upper respiratory tract infection were noted. In study P035, 7 severe AEs for C/T+MTZ group were identified in 5 patients. There were single cases of intestinal obstruction, intra-abdominal fluid collection, abdominal sepsis, bacterial arthritis, lower respiratory tract infection, pneumonia, and increased white blood cell count.

**Table 8-36: Participants With Adverse Events by Maximum Intensity**

| | P034 C/T n (%) | P034 MERO n (%) | P035 C/T+MTZ n (%) | P035 MERO n (%) | Total C/T n (%) | Total MERO n (%) |
|---|---|---|---|---|---|---|
| Participants in population | 100 | 33 | 70 | 21 | 170 | 54 |
| Total | 59 (59) | 20 (61) | 56 (80) | 13 (62) | 115 (68) | 33 (61) |
| Mild | 39 (39) | 14 (42) | 36 (51) | 10 (48) | 75 (44) | 24 (44) |
| Moderate | 15 (15) | 5 (15) | 15 (21) | 3 (14) | 30 (18) | 8 (15) |
| Severe | 5 (5) | 1 (3) | 5 (7) | 0 (0) | 10 (6) | 1 (2) |

Source: 5.3.5.3.3 Integrated Summary of Safety

**Reviewer comments**: *In study P034, 2 subjects developed severe neutropenia which is a well-recognized adverse reaction to β-lactam antibacterial drugs. The other severe AEs are unlikely to be related to C/T and instead are likely related to the progression of the disease.*

**Treatment Emergent Adverse Events and Adverse Reactions**

TEAEs that occurred in 4% or greater of patients receiving ZERBAXA in Studies P035 and P034 are listed in Table 8-37. Of these TEAEs, those that were plausibly related to the use of ZERBAXA are shown in Table 8-38.

**Table 8-37: Treatment Emergent Adverse Events Occurring in 4% or Greater of Pediatric Patients Receiving ZERBAXA in Studies P035 and P034**

| TEAEs | Study P035 Complicated Intra-abdominal Infections | | Study P034 Complicated Urinary Tract Infections, Including Pyelonephritis | |
|---|---|---|---|---|
| | ZERBAXA + MTZ (N=70) n (%) | Meropenem (N=21) n (%) | ZERBAXA (N=100) n (%) | Meropenem (N=33) n (%) |
| Thrombocytosis[1] | 11 (16) | 3 (14) | 9 (9) | 3 (9) |
| Diarrhea | 12 (17) | 5 (24) | 7 (7) | 3 (9) |
| Pyrexia[2] | 9 (13) | 3 (14) | 7 (7) | 1 (3) |
| Leukopenia[3] | 3 (4) | 0 (0) | 8 (8) | 0 (0) |
| Abdominal pain[4] | 8 (11) | 0 (0) | 2 (2) | 1 (3) |
| AST increased | 5 (7) | 1 (5) | 4 (4) | 2 (6) |

| | | | | |
|---|---|---|---|---|
| Vomiting | 7 (10) | 1 (5) | 1 (1) | 1 (3) |
| ALT increased | 4 (6) | 1 (5) | 4 (4) | 2 (6) |
| Anemia[5] | 5 (7) | 0 (0) | 2 (2) | 0 (0) |
| Upper respiratory tract infection | 1 (1) | 0 (0) | 6 (6) | 1 (3) |
| Leukocytosis | 4 (6) | 1 (5) | 1 (1) | 0 (0) |
| Phlebitis[6] | 4 (6) | 0 (0) | 1 (1) | 1 (3) |
| Incision site pain | 4 (6) | 1 (5) | 0 (0) | 0 (0) |
| Wound complication | 4 (6) | 0 (0) | 0 (0) | 0 (0) |
| Tachycardia | 4 (6) | 1 (5) | 0 (0) | 0 (0) |
| Hypertension | 3 (4) | 0 (0) | 0 (0) | 1 (3) |
| Gastritis | 3 (4) | 0 (0) | 0 (0) | 0 (0) |
| Hypokalemia[7] | 3 (4) | 0 (0) | 0 (0) | 0 (0) |
| Bradypnea[8] | 3 (4) | 0 (0) | 0 (0) | 0 (0) |

[1] Includes platelet count increased.
[2] Includes hyperthermia
[3] Includes neutropenia and neutrophil count decreased
[4] Includes upper abdominal pain.
[5] Includes deficiency anemia
[6] Includes superficial phlebitis.
[7] Includes blood potassium decreased.
[8] Includes respiratory rate decreased.

Source: Reviewer produced table based on adae.xpt of Studies 035 and 034

**Table 8-38: Adverse Reactions Occurring in 4% or Greater of Pediatric Patients Receiving ZERBAXA in Studies P035 and P034**

| Adverse Reactions | Study P035 Complicated Intra-abdominal Infections | | Study P034 Complicated Urinary Tract Infections, Including Pyelonephritis | |
|---|---|---|---|---|
| | ZERBAXA + MTZ (N=70) n (%) | Meropenem (N=21) n (%) | ZERBAXA (N=100) n (%) | Meropenem (N=33) n (%) |
| Thrombocytosis[1] | 11 (16) | 3 (14) | 9 (9) | 3 (9) |
| Diarrhea | 12 (17) | 5 (24) | 7 (7) | 3 (9) |
| Pyrexia[2] | 9 (13) | 3 (14) | 7 (7) | 1 (3) |
| Leukopenia[3] | 3 (4) | 0 (0) | 8 (8) | 0 (0) |
| Abdominal pain[4] | 8 (11) | 0 (0) | 2 (2) | 1 (3) |
| AST increased | 5 (7) | 1 (5) | 4 (4) | 2 (6) |
| Vomiting | 7 (10) | 1 (5) | 1 (1) | 1 (3) |
| ALT increased | 4 (6) | 1 (5) | 4 (4) | 2 (6) |
| Anemia[5] | 5 (7) | 0 (0) | 2 (2) | 0 (0) |
| Phlebitis[6] | 4 (6) | 0 (0) | 1 (1) | 1 (3) |
| Hypertension | 3 (4) | 0 (0) | 0 (0) | 1 (3) |

| | | | | |
|---|---|---|---|---|
| Gastritis | 3 (4) | 0 (0) | 0 (0) | 0 (0) |
| Hypokalemia[7] | 3 (4) | 0 (0) | 0 (0) | 0 (0) |
| Bradypnea[8] | 3 (4) | 0 (0) | 0 (0) | 0 (0) |

[1] Includes platelet count increased.
[2] Includes hyperthermia
[3] Includes neutropenia and neutrophil count decreased
[4] Includes upper abdominal pain.
[5] Includes deficiency anemia
[6] Includes superficial phlebitis.
[7] Includes blood potassium decreased.
[8] Includes respiratory rate decreased.
Source: Reviewer produced table based on adae.xpt of Studies 035 and 034

**Reviewer comments:** *Regarding adverse reactions,* (b) (4) *was removed since it is unlikely to be related to the use of ZERBAXA. Leukocytosis and tachycardia are common reactions from acute infection, so unlikely to be related to the use of ZERBAXA. Incision site pain and wound complication are adverse reactions associated with surgery rather than use of ZERBAXA.*

*Hypertension can be related to acute infection but also occurred in adults exposed to ZERBAXA, so it is possibly related to use of ZERBAXA and was included as an adverse reaction in the label. There was one subject (7625A-035-*(b) (6)*) who was reported to have an adverse event of "deficiency anemia." In response to an information request to clarify the specifics of this AE, the Applicant replied that the adverse event occurred on Day 3 and resolved on Day 9 without administration of blood or blood products. Further review of laboratory data shows, hemoglobin decreased from 136 g/L to 101 g/L (normal range: 115 - 150 g/L) and hematocrit decreased from 39.2 % to 29.8 % (normal range 32.5 – 41.5 %).* (b) (4) .

**Laboratory Findings**

In the phase 2 studies, mean changes from baseline over time for clinical chemistry and hematology parameters were generally comparable between the treatment groups. No clinically meaningful changes from baseline over time in any laboratory parameters were observed. The proportion of participants with postbaseline hematology and chemistry measurements that worsened from baseline was generally comparable between treatment groups. Few participants in either treatment group had elevated liver enzymes and no cases of Hy's Law were noted. ALT or AST ≥3 × ULN was reported for 3 participants in the C/T group and 1 participant in the MERO group. Bilirubin ≥1.5 × ULN was reported for 5 participants (present at screening in 4/5 participants) in the C/T group and 1 participant in the MERO group. Most of the liver enzyme elevations occurred at screening or during follow-up and appeared to be transient in nature.

**Reviewer comments:** *Review of the liver enzyme data did not reveal any concern for drug induced liver injury.*

Seroconversion of the direct Coombs' test from negative to positive is a known adverse reaction of ZERBAXA listed in the prescribing information. A higher proportion of participants in the C/T group compared to the MERO group seroconverted from a negative result at baseline to a positive direct Coombs' test result at EOIV. No AEs or laboratory abnormalities suggestive of drug-induced hemolytic anemia were reported for these participants.

**Table 8-39: Cases of Seroconversion to a Positive Direct Coombs Test at End of IV Therapy (EOIV) Visit**

| Direct Coombs Test | P035 | | P034 | | Total | |
|---|---|---|---|---|---|---|
| Treatment | C/T + MTZ n (%) | MERO n (%) | C/T n (%) | MERO n (%) | C/T n (%) | MERO n (%) |
| Seroconversion | 24/53 (45.3) | 4/12 (33.3) | 19/64 (29.7) | 2/23 (8.7) | 43/117 (36.8) | 6/35 (17.1) |

Source: Partially Adapted from page 301 of 5.3.5.3.3 Integrated summary of safety

**Vital Signs**

For the phase 2 studies (P035 and P034), vital sign parameters including heart and respiratory rate, systolic and diastolic blood pressure, and temperature by treatment group were assessed by treatment group and trial day/visit. There were no significant changes in the vital sign measurements between the treatment groups. The mean changes in vital signs from baseline across the scheduled visits were small and generally comparable between the treatment groups.

**Electrocardiograms (ECGs)**

No ECG parameters were tested in studies P035 and P034. In study P010, no clinically significant shifts in ECG parameters were observed in the dosage groups.

**QT**

QT was not measured in studies P034 and P035. 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 ceftolozane/tazobactam. No significant effects of ceftolozane/tazobactam on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected.

**Immunogenicity**

There were no data evaluating the immunogenicity of ZERBAXA submitted in this supplement.

### 8.2.5. Analysis of Submission-Specific Safety Issues

Predefined adverse events of clinical interest for both study P035 and P034 were elevated liver enzymes meeting specific criteria (DILI) and events of ZERBAXA overdose. No adverse events of clinical interest were reported in either study.

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

There were no COA data in the pediatric studies P035 and P034.

### 8.2.7. Safety Analyses by Demographic Subgroups

The number of patients who developed TEAEs by age group for studies P035 (cIAI) and P034 (cUTI) are listed in Table 8-40 and Table 8-41, respectively.

**Table 8-40. Treatment Emergent Adverse Events by Age Group and Treatment Arm in Study 035**

| | ZERBAXA + MTZ (%) | MERO (%) |
|---|---|---|
| Group 5: Birth to < 3 (Months) | 1/1 (100) | 0* |
| Group 4: 3 (Months) to < 2 (Years) | 0/1 (0) | 0* |
| Group 3: 2 to < 6 (Years) | 18/22 (82) | 4/7 (57) |
| Group 2: 6 to < 12 (Years) | 26/30 (87) | 6/9 (67) |
| Group 1: 12 to < 18 (Years) | 11/16 (69) | 3/5 (60) |
| Total | 56/70 (80) | 13/21 (60) |

* No subjects were enrolled.
Source: Reviewer generated from Table 14.3-2 of CSR P035

**Table 8-41: Treatment Emergent Adverse Events by Age Group and Treatment Arm in Study 034**

| | ZERBAXA (%) | MERO (%) |
|---|---|---|
| Group 5: Birth to < 3 (Months) | 9/15 (60) | 3/6 (50) |
| Group 4: 3 (Months) to < 2 (Years) | 15/24 (63) | 5/7 (71) |
| Group 3: 2 to < 6 (Years) | 11/22 (50) | 4/7 (57) |
| Group 2: 6 to < 12 (Years) | 13/24 (54) | 4/8 (50) |
| Group 1: 12 to < 18 (Years) | 11/15 (73) | 4/5 (80) |
| Total | 59/100 (59) | 20/33 (61) |

Source: Reviewer generated from Table 14.3-2 of CSR P034

**Reviewer comments:** *The rates of adverse events were similar between the age groups. For study P035, only a small number of patients were enrolled in groups 4 and 5 for both C/T and MERO groups.*

### 8.2.8. Specific Safety Studies/Clinical Trials

In Study P010, 11 subjects (29.7%) experienced at least 1 AE and all AEs were either mild or moderate in intensity. Anemia, diarrhea, and hypokalemia were the only AEs reported in 2 subjects each. Three subjects (8.1%) experienced SAEs. There were no severe AEs, deaths, or AEs leading to discontinuation of study treatment. There were no events of hypersensitivity reactions or hemolytic disorders, or any events involving CDAD.

**Reviewer comments:** *The 3 SAEs were pneumonia, infective pulmonary exacerbation of cystic fibrosis, and central venous catheter associated fungal sepsis which are all unlikely to be related to ZERBAXA. The overall safety profile in Study P010 is consistent with findings in Study P035 or P034.*

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

No new carcinogenicity studies were submitted. Refer to section 4.3 of the clinical review of the original NDA by Dr. Maria Allende. Previously, ceftolozane and tazobactam were not found to have mutagenic potential in several *in vivo* and *in vitro* genetic toxicity assays. There have been no safety signals related to human carcinogenicity. In general, antibacterial drugs are typically administered as a single course of treatment over a limited period of time for an acute illness; therefore, prolonged exposure is not anticipated**.**

**Human Reproduction and Pregnancy**

No new information regarding human reproduction and pregnancy was submitted. The safety studies of ZERBAXA in pediatric patients in cIAI (P035) and cUTI (P034) 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 studies under review were both pediatric studies. The patients 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 studies P034 and P035.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

Review of the postmarketing safety reports did not reveal any new safety issues related to use in pediatric patients.

On December 10, 2021, Health Canada posted an alert on their website stating that they have started safety reviews regarding the cephalosporin class of drugs, including ceftolozane and tazobactam (ZERBAXA®), and the potential safety issue of "seizures." [11]

The following are cases of seizure obtained from periodic adverse drug experience report: One seizure case was reported for the reporting period of (b) (6), through (b) (6). Two seizure cases were reported for the reporting period of (b) (6), through (b) (6). Three seizure cases were reported for the reporting period of (b) (6) through (b) (6). Three seizure cases were reported for the reporting period of (b) (6) through (b) (6). Five seizure cases were reported for the reporting period of (b) (6), through (b) (6).

**Reviewer comments:** *No events of seizures were reported in the studies P034 and P035.*

**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.

#### 8.2.11. Integrated Assessment of Safety

The assessment of the safety of ZERBAXA for the treatment of cIAI and cUTI in pediatric patients from birth to less than 18 years of age is primarily based on the clinical studies P035 and P034 which evaluated the safety of ZERBAXA in pediatric patients with cIAI and cUTI, respectively. The overall incidence of AEs with patients who received ZERBAXA or ZERBAXA + MTZ were comparable with those who received meropenem. AEs were generally mild to moderate in intensity. Those events that were severe in intensity, SAEs, or discontinuations were due to AEs that were mostly unrelated to ZERBAXA. No deaths were reported. Also, no clinically significant changes in vital signs, physical examination findings, or laboratory results were reported except conversion of the Coombs' test to positive which is already listed in the ZERBAXA prescribing information. The overall safety profile of ZERBAXA in pediatric patients from birth to less than 18 years of age was similar to the safety profile in adults with cIAI and cUTI, treated with ZERBAXA. No new safety signals were identified.

## 8.3. Statistical Issues

Since Studies P034 and P035 were descriptive studies with limited numbers of subjects, particularly in the meropenem arm, they were not adequately powered for hypothesis testing.

[11] https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/new.html

Therefore, statistical inferences could not be drawn. Since these studies also did not have any specified 'win criteria', the interpretation of efficacy findings was limited.

There were also some concerns that clinical success and microbiological success rates were substantially lower in the C/T arm (Study 034) and C/T+MTZ arm (Study 035) versus the MERO arm at the TOC visit (as well as at other visits). However, based on the adult studies submitted in the original NDA, Studies -03&04 for cUTI and –8&09 for cIAI, these rates were not considered to be unusually low. Therefore, the less favorable treatment differences observed in Studies P034 and P035 may have been largely due to higher than expected success rates in the MERO arm. In addition, there appeared to be higher rates of indeterminate outcomes in the C/T and C/T+ MTZ arms versus the meropenem arm in these studies.

Other limitations in the studies included the definitions of the mMITT populations which did not require the baseline pathogen to be susceptible to both study drugs. However, this was not a major concern since in both studies, all or nearly all subjects had pathogens which were susceptible to both study drugs. Another issue was related to the timing of the follow-up visits which were based on the last dose of study drug rather than the time from randomization. This can result in differences in the duration of exposure to study drug related to differences in study drug efficacy, which could influence efficacy assessments. However, the mean durations of exposure to study drug were observed to be comparable between study arms in both studies.

Another limitation noted was that most participants in Study P035 did not have postbaseline intra-abdominal cultures, and therefore the majority of microbiologic outcomes were based on presumed eradication (i.e., clinical success in participants who did not have follow-up postbaseline intra-abdominal cultures) rather than documented eradication of the infecting organism. However, not having postbaseline cultures is not unusual in cIAI trials.

## 8.4. Conclusions and Recommendations

The reviewers conclude that the Applicant has submitted adequate evidence to recommend the approval of ZERBAXA as a safe and effective treatment for cIAI and cUTI in pediatric patients from birth to less than 18 years of age. The determination of the effectiveness of ZERBAXA in the treatment of cIAI and cUTI in pediatric patients is primarily based on extrapolation of efficacy data from controlled trials of ZERBAXA for treatment of cIAI and cUTI in adults and PK data from P010, P034, and P035. The assessment of the safety of ZERBAXA in the treatment of cIAI and cUTI is primarily based on data from the pediatric clinical studies P034 and P035 and PK study P010. The overall safety profile of ZERBAXA in pediatric patients from birth to less than 18 years of age was similar to the safety profile in adults treated with ZERBAXA for cIAI and cUTI, and no new safety signals were identified.

# 9 Advisory Committee Meeting and Other External Consultations

There were no advisory committees meeting convened for this sNDA.

APPEARS THIS WAY ON ORIGINAL

# 10 Pediatrics

The current submissions address the safety of ZERBAXA for: (1) the treatment of cIAI in pediatric patients from birth to less than 18 years of age (S-012), and (2) the treatment of cUTI in pediatric patients from birth to less than 18 years of age (S-011), and fulfill the PREA postmarketing requirements for assessments in pediatric patients. Supplement 011 [PMR 2809-1] was submitted on June 21, 2021, and Supplement 012 [PMR 2809-2] on July 2, 2021, to expand the cUTI and cIAI indications, respectively, to the pediatric population.

At the Pediatric Review Committee (PeRC) meeting on March 22, 2022, concerns with dosing of ZERBAXA in neonates was discussed. First, there is no standard equation to assess the renal function of pediatric patients less than 1 year of age. Secondly, pediatric patients born at term or pre-term may not have an eGFR of 50 mL/min/1.73 $m^2$ or greater in the first few months of life. For Studies P034 and P035, pediatric patients with an eGFR <50 mL/min/1.73 $m^2$ were excluded. Therefore, no dosing guidance could be made for pediatric patients with an eGFR <50 mL/min/1.73 $m^2$.

The Division of Pediatric and Maternal Health (DPMH) was consulted regarding the above mentioned issues. (b) (4) DPMH agreed that there is no standard equation to assess a pediatric patient's renal function in neonates. Based on DPMH's recommendation, the multi-disciplinary review team recommended that the Applicant include language in the ZERBAXA labeling noting that prescribers use an "age-appropriate equation" to assess a pediatric patient's renal function (b) (4) For infants born pre-term, this extends past 4 months with those born at the earliest gestational ages taking the longest to reach this GFR threshold[13].

(b) (4)

[13] Vieux R, Hascoet JM, Merdariu D, Fresson J, Guillemin F. Glomerular filtration rate reference values in very preterm infants. Pediatrics. 2010;125(5):e1186-e1192. doi:10.1542/peds.2009-1426

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

**Prescribing information**
Key significant labeling changes made to the PI submitted by the Applicant on June 21, 2021, (Supplement 11) and July 2, 2021, (Supplement 12), respectively, are described in Table 11-1 below. DPMH was consulted and contributed to the recommendations on the pediatric dosing information.

**Table 11-1: Summary of Significant Labeling Changes in this Review**

| Section/subsection | Applicant Proposed Labeling | Labeling Modifications |
|---|---|---|
| 1 INDICATIONS AND USAGE (1.1 and 1.2) | • Pediatric patients were added to the cIAI and cUTI indications. | • Added a specific pediatric age group in the indication statement (i.e., birth to less than 18 years old) for consistency with the approved pediatric age group specified in the other sections of the PI. |
| **Reviewer comment:** *The rationale for describing the approved age groups in the indication as "pediatric patients birth to less than 18 years old" includes the following. (1) Although 21 CFR 201.57(c)(9)(iv)(A) defines pediatric patients as birth to 16 years (and CDER has generally considered the upper age group to encompass the entire 16th year), 21 CFR 201.57(c)(9)(iv)(G) permits use of an appropriate, alternative statement if statements described in paragraphs (A) through (F) of 21 CFR 201.57(c)(9)(iv) are not appropriate or relevant to the drug's labeling. (2) The information in the Indications and Usage section should use terminology that is clinically relevant and scientifically valid. Accordingly, "pediatric patients birth to less than 18 years old" is consistent with the clinical studies definition of the pediatric patients. Refer to subsection 8.1 for additional details.* | | |
| 2 DOSAGE AND ADMINISTRATION (2.2) (2.4) | • Added ZERBAXA dosage information for pediatric patients (birth to less than 18 years of age) with cIAI and cUTI with eGFR greater than 50 mL/min/1.73 $m^2$ .<br>• Footnote included the statement (b) (4) [redacted] | • Added the following statements to clarify that:<br>• ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL/min/1.73$m^2$ or less, *and*<br>• There is insufficient information to recommend a dosage regimen for pediatric patients with HABP/VABP<br>• Footnote revised to read as "Estimated GFR using an age-appropriate equation for use in the pediatric population" based on recommendation from |

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| | (b) (4)<br>• Added dosage adjustment for ZERBAXA in pediatric patients (birth to less than 18 years of age with eGFR <50 mL/min/1.73 $m^2$ (b) (4) has not been determined. | DPMH. Refer to Subsection 6.1 and Section 10.<br>• Revised to ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL mL/min/1.73 $m^2$ or less. |
| 6 ADVERSE REACTIONS (6.1) | • Added clinical trial information for pediatric patients with cIAI and cUTI, including pyelonephritis.<br>• The Applicant's adverse reaction table (Table 8) included adverse reactions that occurred in (b) (4) % or greater of pediatric patients receiving ZERBAXA in Phase 2 cIAI and cUTI clinical trials.<br>• In the HIGHLIGHTS section, the Applicant listed adverse reactions (b) (4) % in either cIAI or cUTI indication as most common adverse reactions. | • The adverse reaction table (Table 8) was modified to include adverse reactions that occurred in >4% of subjects and did not consider investigator-determined relatedness. Adverse reactions that were listed under different preferred terms were combined when they referred to the same medical concept. Refer to section 8.2.4 for additional details.<br>• In the HIGHLIGHTS section, the most common adverse reactions in pediatric patients were modified based on the same rationale applied for Table 8. Also, modified the definition of most common adverse reactions as adverse reactions ≥7 % in either cIAI or cUTI. |
| 8 USE IN SPECIFIC POPULATIONS (8.4) (8.6) | • Added information on pediatric use.<br>• Added information on patients with renal impairment to state that no dose adjustment has been | • Based on DPMH input, added the following statement: ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL/min/1.73 $m^2$ or less. Pediatric patients born at term or pre-term may not have an eGFR of 50 mL/min/1.73$m^2$ or greater at birth, |

| | | |
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| | established in pediatric patients aged birth to less than 18 years of age with eGFR <50 mL/min/1.73 $m^2$ (b) (4) | or within the first few months of life. Refer to Section 10 for additional details.<br>• Revised the statement on pediatric patients with renal impairment to read as follows: "No dose adjustment has been established in pediatric patients aged birth to less than 18 years of age with eGFR 50 mL/min/1.73 $m^2$ or less." Refer to Subsections 6.2, 8.1.3, 8.1.1 (i.e., Table 8-23), and 15.2.1.2 for additional details. |
| **Reviewer comment:** *The pediatric use labeling language proposed by the Applicant was modified by adding information on the basis of approval to be consistent with the labeling recommendations in the FDA Guidance for Industry: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (March 2019)[14].* | | |
| 12 CLINICAL PHARMACOLOGY (12.3) | • Added information on pediatric patients. | • Modifications were made to the presentation of the quantitative information in the tabular format.<br>• Applicant initially proposed to list the PK parameter summary using Groups 2 and 3 as (b) (4) to <12 years old and 2 to (b) (4) years old, respectively. During the labeling discussions, the Applicant proposed to revise Groups 2 and 3 as 6 to <12 years old and 2 to <6 years old. This proposal was found to be reasonable.<br>Refer to Subsections 6.2 and 15.2.3 for additional details. |
| **Reviewer comment:** *To be consistent with the adult PopPK parameter summary, modifications were made to the presentation of the quantitative information in the tabular format presented by the Applicant (e.g., change from geometric mean (GCV%) to arithmetic mean (SD).* | | |
| 14 CLINICAL STUDIES (14.1 and 14.2) | • Added clinical study information to support the use of ZERBAXA in pediatric patients for the | • Added confidence intervals for the treatment difference to the tables containing the response rates. |

[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good

| | | |
|---|---|---|
| | treatment of cIAI and cUTI. | |
| **Reviewer comment:** *In the pediatric patients section, the treatment difference and 95 % confidence intervals based on the Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel weights were added to the clinical response rate table for cIAI and the clinical and microbiological response rates table for cUTI. Refer to Subsection 8.1 for additional details* | | |

# 12 Risk Evaluation and Mitigation Strategies (REMS)

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

# 13 Postmarketing Requirements and Commitment

Please see Section 3 Regulatory Background for details regarding PMRs 2809-1 and 2809-2. The Applicant can be released from these PMRs.

Of note, the following PMR[15] remains outstanding and is intended to be fulfilled by a Pediatric Written Request[16].

3637-1 Conduct a safety and pharmacokinetic study in HABP/VABP in children from birth to less than 18 years of age.

Final Protocol Submission: Submitted
Study/Trial Completion: 04/2023
Final Report Submission: 11/2023

# 14 Division Director (DAI) Comments

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

[15] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/206829Orig1s008ltr.pdf
[16] NDA 206829, SDN 769, February 8, 2022, Written Request Letter

# 15 Appendices

## 15.1. Financial Disclosure

**Covered Clinical Study (Name and/or Number):** Study P034 and Study P035

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 380 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>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 Studies

### 15.2.1.1. Pediatric clinical trial with a single dose

**Study P010MK7625A (P010)**

This was a phase 1 non-comparative, open-label study to characterize the PK, safety, and tolerability of a single IV dose of C/T (infused over 60 ± 10 minutes) in hospitalized pediatric patients receiving standard of care antibiotic therapy for a proven or suspected gram-negative infection (n = 36) or for peri-operative prophylaxis (n = 1).

A total of 37 patients (birth to <18 years old) were enrolled in 6 age based treatment groups (Groups 1-6) and received C/T treatment (Table 15-1). All 37 patients were included in the safety population (Table 15-1).

The initial pediatric doses of C/T were chosen based on adult PK data with the objective of achieving the exposure levels seen in adults receiving the therapeutic dose. After 3 subjects in each age group received the initial dose of C/T, an interim analysis of PK and safety data was conducted in each age group to determine if the initial dose was appropriate. The appropriateness was determine based on the absence of a safety signal and TOL exposures (attain targets of 30% time > MIC of 8 µg/mL and $AUC_{0\text{-}inf}$ of ~200 µg*h/mL , but not to exceed $AUC_{ss}$ of 1100 total daily exposure). Following an interim analysis conducted for Group 4 subjects, TOL AUC target was changed from approximately 200 µg*h/mL to 130 to 175 µg*h/mL for Groups 5-6. No TAZ PK target was initially specified however it was set at the $AUC_{0\text{-}inf}$ of 24 µg*h/mL for Groups 5-6.

For PK assessments, blood samples were collected at 5 time points (0, 1 [end of infusion], 2, 4, and 6 hours after the start of infusion) with an optional 0.5 hour time point in Groups 1-4. For Groups 5 and 6, 3 PK samples (1, 2, and 6 hours after start of infusion) were collected. Collected samples were analyzed for TOL and TAZ concentrations to determine plasma PK parameters for TOL and TAZ using a noncompartmental analysis (Table 15-2 and Table 15-3).

**Table 15-1: Baseline Demographics of PK Evaluated Subjects Presented as Mean (SD)**

| | 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[&] [>32 weeks GA] to <3 months | Group 6 Birth[&] [≤32 weeks GA] to <3 months | |
|---|---|---|---|---|---|---|---|---|---|
| | n = 6 | n = 6 | n = 3 | n = 3 | n = 1 | n = 5 | n = 7 | n = 2 | n = 4 |
| Dose | 1000 mg | 18 mg/kg | 18 mg/kg | 30 mg/kg | 18 mg/kg | 30 mg/kg | 20 mg/kg | 12 mg/kg | 20 mg/kg |
| Weight (kg) | 52.0 (7.7) | 29.9 (8.6) | 20.7 (5.7) | 17.3 (5.1) | 10.7 (-) | 8.9 (9) | 4.1 (0.7) | 1.3 (0.3) | 2.7 (0.7) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Height (cm) | 158 (5) | 130 (6) | 113 (9) | 103 (10) | 79 (-) | 69 (9) | 53 (5) | 37 (1) | 46 (4) |
| eGFR (mL/min/1.73 $m^2$)[†] | 144 (42) | 135 (28) | 131 (9) | 118 (29) | 181 (-) | 122 (42) | 80 (16) | 31 (5) | 87 (15) |
| Gender (% male) | 17 | 67 | 67 | 33 | 100 | 60 | 57 | 100 | 25 |

GA=Gestational Age
[†]Estimated GFR was determined using the bedside Schwartz equation with the inclusion criteria set for Groups 1-4 at ≥80 ml/min/$m^2$, Group 5 at ≥50 ml/min/$m^2$, and Group 6 at ≥20 ml/min/$m^2$.
[&]Groups 5 and 6 patients were of at least 7 days postnatal age.
*Source: Adapted from clinical study report P010MK7625A (ADAM-ADPP), and 05qwch legacy datasets (cpkpool, tpkpool).*

**Table 15-2: TOL Plasma PK Parameters Following a Single IV Dose in Subjects With Proven or Suspected Gram-Negative Infection, Presented as Geometric Mean (GM 95% CI)**

| | 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[&] [>32 weeks GA] to < 3 months | Group 6 Birth[&] [≤32 weeks GA] to < 3 months | |
|---|---|---|---|---|---|---|---|---|---|
| | n = 5 | n = 6 | n = 3 | n = 3 | n = 1 | n = 5 | n = 6 | n = 2 | n = 3 |
| Dose | 1000 mg | 18 mg/kg | 18 mg/kg | 30 mg/kg | 18 mg/kg | 30 mg/kg | 20 mg/kg | 12 mg/kg | 20 mg/kg |
| $C_{max}$ (µg/mL) | 64 (50, 80) | 56 (45, 70) | 51 (38, 70) | 97 (71, 131) | 99 (30, 86) | 91 (72, 116) | 45 (36, 56) | 35 (24, 51) | 45 (33, 61) |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 133 (104, 171) | 107 (86, 135) | 99 (72, 137) | 186 (135, 255) | 103 (59, 180) | 202 (158, 259) | 164 (131, 205) | 165 (112, 244) | 137 (100, 189) |
| $V_{ss}$ (L/kg)[b] | 0.27 (26) | 0.30 (22) | 0.33 (16) | 0.31 (20) | 0.28 (-) | 0.34 (21) | 0.39 (13) | 0.34 (37) | 0.39 (27) |
| CL ((L/h/)kg)[b] | 0.15 (27) | 0.17 (21) | 0.18 (3.8) | 0.16 (31) | 0.18 (-) | 0.15 (43) | 0.12 (36) | 0.07 (32) | 0.15 (7) |
| $t_{1/2}$ (h)[b] | 1.5 (17) | 1.3 (10) | 1.3 (14) | 1.5 (36) | 1.3 (-) | 1.6 (69) | 2.2 (38) | 3.1 (1) | 1.7 (30) |

[a] TOL dose was not to exceed a fixed maximum dose of 1000 mg.
[b]Statistics for, $V_{ss}$, CL, $t_{1/2}$ were geometric mean (percent geometric CV%); (-): not available.
GA=Gestational Age, [&]Groups 5 and 6 patients were of at least 7 days postnatal age.
Three subjects (Groups 1 [n =1], 5 [n = 1] and 6 [n = 1]) were excluded from PK population, because of sample switch, improper dose administration, and insufficient plasma volume, respectively.
*Source: Adapted from clinical study report P010MK7625A and 05qwch legacy dataset and program (cpkpool, exposure-ind).*

**Table 15-3: TAZ Plasma PK Parameters Following a Single IV Dose in Subjects With Proven or Suspected Gram-Negative Infections, Presented as Geometric Mean (GM 95% CI)**

| | 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[&] [>32 weeks GA] to < 3 months | Group 6 Birth[&] [≤32 weeks GA] to < 3 months | |
|---|---|---|---|---|---|---|---|---|---|
| | n = 5 | n = 6 | n = 3 | n = 3 | n = 1 | n = 5 | n = 7 | n = 2 | n = 4 |

| Dose | 500 mg | 9 mg/kg | 9 mg/kg | 15 mg/kg | 9 mg/kg | 15 mg/kg | 10 mg/kg | 6 mg/kg | 10 mg/kg |
|---|---|---|---|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | 14 (9, 23) | 9 (6, 15) | 16 (8, 30) | 25 (13, 47) | 12 (4, 35) | 22 (14, 37) | 12 (7, 18) | 7 (3, 15) | 12 (6, 23) |
| $AUC_{0\text{-}inf}$ (h*µg/mL) | 18 (13, 24) | 10 (7, 16) | 18 (12, 27) | 29 (19, 44) | 15 (7, 31) | 30 (22, 41) | 25 (18, 34) | 78 (38, 161) | 22 (15, 34) |
| $V_{ss}$ (L/kg)[b] | 0.5 (70) | 0.7 (30) | 0.5 (32) | 0.5 (49) | 0.4 (-) | 0.6 (34) | 0.7 (20) | 0.4 (-) | 0.7 (29) |
| CL ((L/h/)kg)[b] | 0.6 (54) | 0.9 (23) | 0.5 (42) | 0.5 (45) | 0.6 (-) | 0.5 (35) | 0.4 (34) | 0.1 (-) | 0.5 (25) |
| $t_{1/2}$ (h)[b] | 0.7 (39) | 0.5 (3) | 0.7 (30) | 0.8 (34) | 0.5 (-) | 0.8 (85) | 1.1 (32) | 3.0 (-) | 0.9 (20) |

[a] TAZ dose was not to exceed a fixed maximum dose of 500 mg
[b] Statistics for $C_{last}$, $V_{ss}$, CL, $t_{1/2}$ were geometric mean (percent geometric CV%); (-): not available.
GA=Gestational Age, [&]Groups 5 and 6 patients were of at least 7 days postnatal age.
Three subjects (Groups 1 [n =1], 5 [n = 1] and 6 [n = 1]) were excluded from PK population, because of sample switch, improper dose administration, and insufficient plasma volume, respectively.
*Source: Adapted from clinical study report P010MK7625A and 05qwch legacy dataset and program (tpkpool, exposure-ind).*

### 15.2.1.2. Pediatric clinical trial with a multiple dose regimen

**Study MK-7625A-034 (P034)**

This was a phase 2, randomized, active comparator-controlled, multicenter, double-blind clinical study comparing C/T vs. meropenem (MERO) in pediatric subjects with cUTI, including pyelonephritis. In this study, the safety and tolerability of C/T was compared to MERO 20 mg/kg IV every 8 hours (maximum 1 g/dose) in subjects from birth (>32 week gestational age and ≥7 days postnatal) to <18 years of age with cUTI, including pyelonephritis and a baseline eGFR ≥50 mL/min/1.73 $m^2$ based on the bedside Schwartz equation. The doses for C/T were 1.5 g IV every 8 hours (1 hour infusion) for subjects 12 years to <18 years or 30 mg/kg (TOL 20 mg/kg + TAZ 10 mg/kg ) every 8 hours (1 hour infusion) for subjects <12 years of age. The maximum dose was 1.5 g every 8 hours.

In the C/T group, a total of 101 patients (birth to <18 years old) were enrolled in 5 age based treatment groups (Groups 1-5). From the enrolled patients 100 received 1 dose and were included in the safety population and 89 were included in the PK population (Table 15-4).

The exploratory objective of this study was to evaluate the PK of TOL and TAZ at steady-state (after at least 6 doses) in this target population (i.e., pediatrics with cUTI) and update the existing respective pediatric popPK models. The popPK models were used to perform simulations to evaluate PTA at suitable doses. In addition, the PK data aided in the assessment of the clinical relationship between C/T and efficacy in this pediatric population. PK blood samples were collected at 3 time points: at the end of infusion, between 4 and 5 hours post start of infusion, and between 7 and 8 hours post start of infusion but prior to start of next dose. The collected samples were analyzed for TOL and TAZ concentrations to determine plasma PK parameters for each of the drugs using PopPK modeling (Table 15-5 and Table 15-6). See Section 15.2.3 for details on the PopPK modeling.

**Table 15-4: Baseline Demographics of PK Population Subjects Presented as Mean (SD)**

| | Group 1 12 to 18 years n = 14 | Group 2 7 to <12 years n = 15 | Group 3 2 to <7 years n = 25 | Group 4 3 mo to <2 years n = 23 | Group 5 Birth to <3 months n = 14 |
|---|---|---|---|---|---|
| Weight (kg) | 51 (9) | 35 (13) | 17 (4) | 9 (2) | 5 (1) |
| eGFR (mL/min/1.73 $m^2$) † | 133 (29) | 148 (28) | 136 (47) | 137 (72) | 84 (32) |
| Gender (%Males) | 36 | 7 | 24 | 48 | 86 |

†Estimated GFR was determined using the bedside Schwartz equation.
*Source: Adapted from clinical study report P034MK7625A, and 05qwch legacy datasets (cpkpool and tpkpool).*

**Table 15-5: TOL Plasma PK Parameters Following a Multiple IV Dose in Subjects With cUTI, Presented as Geometric Mean (GCV%)**

| | Group 1 12 to 18 years n = 14 | Group 2 7 to <12 years n = 15 | Group 3 2 to <7 years n = 25 | Group 4 3 mo to <2 years n = 23 | Group 5 Birth to <3 months n = 14 |
|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | 66 (34) | 59 (38) | 56 (40) | 47 (40) | 42 (28) |
| $AUC_{0-8}$ (h*µg/mL) | 168 (35) | 137 (36) | 127 (37) | 119 (41) | 139 (29) |
| $V_{ss}$ (L/kg) | 0.30 (29) | 0.32 (36) | 0.32 (43) | 0.39 (45) | 0.51 (30) |
| CL ((L/h/)kg) | 0.12 (26) | 0.14 (36) | 0.16 (37) | 0.17 (42) | 0.15 (27) |
| $t_{1/2}$ (h) | 2.3 (16) | 2.0 (22) | 1.8 (25) | 1.9 (34) | 2.6 (24) |

*Source: Adapted from 05qwch legacy dataset and program (cpkpool, exposure-ind).*

**Table 15-6: TAZ Plasma PK Parameters Following a Multiple IV Dose in Subjects With cUTI, Presented as Geometric Mean (GCV%)**

| | Group 1 12 to 18 years n=14 | Group 2 7 to <12 years n=15 | Group 3 2 to <7 years n=25 | Group 4 3 mo to <2 years n=23 | Group 5 Birth to <3 months n=14 |
|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | 22 (29) | 19 (40) | 18 (31) | 17 (50) | 24 (39) |
| $AUC_{0-8}$ (h*µg/mL) | 33 (33) | 26 (32) | 25 (28) | 27 (40) | 42 (41) |
| $V_{ss}$ (L/kg) | 0.30 (41) | 0.25 (75) | 0.31 (49) | 0.34 (80) | 0.30 (51) |
| CL ((L/h/)kg) | 0.12 (26) | 0.14 (36) | 0.16 (37) | 0.17 (42) | 0.15 (27) |
| $T_{1/2}$ (h) | 1.3 (26) | 1.2 (29) | 1.0 (24) | 1.0 (37) | 1.1 (42) |

*Source: Adapted from 05qwch legacy datasets and program (tpkpool, exposure-ind).*

**Study MK-7625A-035 (P035)**

This was a phase 2, randomized, active comparator-controlled, multicenter, double-blind clinical study comparing C/T plus metronidazole (MTZ) vs. MERO in pediatric subjects with cIAI. In this study, the safety and tolerability of C/T plus MTZ was compared to MERO 20 mg/kg IV every 8 hours (maximum 1 g/dose) in subjects from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cIAI and a baseline eGFR ≥50 mL/min/1.73 $m^2$ based on the bedside Schwartz equation. The doses for C/T were 1.5 g IV every 8 hours (1 hour infusion) for subjects 12 years to <18 years or 30 mg/kg (maximum 1.5 g) every 8 hours (1 hour infusion) for subjects <12 years of age, while MTZ was 10 mg/kg (maximum 1.5 g/day) IV every 8 hours for subjects >28 days of age to <18 years of age. Sites were provided the choice of suggested

MTZ doses for subjects ≤28 days of age or site-specific standard of care dosing at the investigator's discretion.

In the C/T + MTZ group, a total of 71 patients (birth to <18 years old) were enrolled in 5 age based treatment groups (Groups 1-5). From the enrolled patients, 70 received 1 dose and were included in the safety population and 66 were included in the PK population (Table 15-7) which now consisted of 3 age based treatment groups (Groups 1-3). The study originally planned to enroll patients birth to <2 years, however, due to enrollment challenges, the Applicant was not able to collect sufficient PK data in subjects from birth (>32 weeks gestational age and ≥7 days postnatal) to <2 years.

The exploratory objective was to evaluate the steady-state PK of TOL and TAZ (after at least 6 doses) in this target population (i.e., pediatrics with cIAI) and update the existing respective pediatric popPK models. The popPK models were used to perform simulations to evaluate PTA at suitable doses. PK blood samples were collected at 3 time points: at the end of infusion, between 4 and 5 hours post start of infusion, and between 7 and 8 hours post start of infusion but prior to start of next dose. Of note, one subject from Group 1 (12- <18 y) that was enrolled and had PK collected, exhibited a baseline eGFR of ~46 ml/min/1.73 $m^2$ in one out of two renal measurements. The other eGFR measurement was greater than 50 ml/min/1.73 $m^2$. The collected samples were analyzed for TOL and TAZ concentrations to determine plasma PK parameters for TOL and TAZ using a PopPK modeling (Table 15-8 and Table 15-9). See Section 15.2.3 for details on the PopPK modeling.

**Table 15-7: Baseline Demographics of PK Population Subjects Presented as Mean (SD)**

| | Group 1<br>12 to 18 years<br>n = 16 | Group 2<br>7 to <12 years<br>n = 27 | Group 3<br>2 to <7 years<br>n = 23 |
|---|---|---|---|
| Weight (kg) | 60 (17) | 32 (8) | 18 (5) |
| eGFR (mL/min/1.73 $m^2$) † | 157 (61) | 171 (46) | 191 (100) |
| Gender (%Males) | 75 | 67 | 56 |

†Estimated GFR was determined using the bedside Schwartz equation.
*Source: Adapted from clinical study report P035MK7625A, dataset (ADAM-ADLB), 05qwch legacy datasets (cpkpool and tpkpool).*

**Table 15-8: TOL Plasma PK Parameters Following a Multiple IV Dose in Subjects With cIAI, Presented as Geometric Mean (GCV%)**

| | Group 1<br>12 to 18 years<br>n=16 | Group 2<br>7 to <12 years<br>n=27 | Group 3<br>2 to <7 years<br>n=23 |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 47 (50) | 51 (32) | 42 (34) |
| $AUC_{0-8}$ (h*µg/mL) | 115 (43) | 113 (28) | 96 (27) |
| $V_{ss}$ (L/kg) | 0.35 (48) | 0.34 (32) | 0.41 (35) |
| CL ((L/h/)kg) | 0.15 (42) | 0.18 (27) | 0.21 (28) |
| $t_{1/2}$ (h) | 2.1 (19) | 1.8 (13) | 1.7 (16) |

Note: 1 subject from Group 5 (~ 1 month old) had the following TOL PK values: $AUC_{0-8}$ (173 µg*h/mL), $C_{max}$ (43 µg/mL), $t_{1/2}$ (3.2 h), CL (0.13 L/h/kg), Vss (0.56 L/kg).
*Source: Adapted from 05qwch legacy dataset and program (cpkpool, exposure-ind).*

**Table 15-9: TAZ Plasma PK Parameters Following a Multiple IV Dose in Subjects With Complicate Intra-abdominal Infection, Presented as Geometric Mean (GCV%)**

| | Group 1<br>12 to 18 years<br>n = 16 | Group 2<br>7 to <12 years<br>n = 27 | Group 3<br>2 to <7 years<br>n = 23 |
|---|---|---|---|
| $C_{max}$ (µg/mL) | 20 (48) | 20 (35) | 16 (41) |
| $AUC_{0-8}$ (h*µg/mL) | 29 (46) | 30 (25) | 23 (28) |
| $V_{ss}$ (L/kg) | 0.29 (39) | 0.30 (52) | 0.36 (60) |
| CL ((L/h/)kg) | 0.30 (38) | 0.34 (24) | 0.43 (28) |
| $t_{1/2}$ (h) | 1.2 (17) | 1.1 (14) | 1.0 (19) |

Note: 1 subject from Group 5 (~1 month old) had the following TAZ PK values: $AUC_{0-8}$ (70 µg*h/mL), $C_{max}$ (31 µg/mL), $t_{1/2}$ (1.4 h), CL (0.16 L/h/kg), Vss (0.30 L/kg).
*Source: Adapted from popPK report (05qwch), 05qwch legacy datasets and program (tpkpool, exposure-ind).*

### 15.2.2. Summary of Bioanalytical Method Validation and Performance

The bioanalytical method validation report and sample analysis reports for the quantitation of TOL, TAZ, and TAZ-M-1 were reviewed and deemed acceptable. TAZ-M-1 is a pharmacologically inactive metabolite formed via hydrolysis of the TAZ beta-lactam ring. Bioanalytical methods and results are summarized in Table 15-10 and Table 15-11.

An inspection by the Office of Study Integrity and Surveillance (OSIS) was requested at the filing meeting for the two Clinical Research Organizations (CRO) that performed the bioanalytical method validations and performances for study P010 and P034/035. OSIS only remotely inspected one of the CROs (b) (4), previously (b) (4)), as the other CRO ((b) (4)) was previously inspected in (b) (4). Based on the outcome of the remote record review, OSIS states that the audited bioanalytical method validation and performance for study P010 are reliable.

**Table 15-10: Bioanalytical Method Validation Summary**

| **Validation Report #** | (b) (4)14B-0058 | (b) (4)-1756-18 |
|---|---|---|
| **Drug Analytes** | ceftolozane, tazobactam, tazobactam-M-1 | ceftolozane, tazobactam, tazobactam-M-1 |
| **CRO** | (b) (4) | (b) (4) |
| **Method of Detection** | LC-MS/MS | LC-MS/MS |
| **Biological Matrix** | Human plasma | Human Plasma |
| **Anticoagulant** | Sodium heparin | Lithium heparin |
| **Extraction Method** | Juvenile human plasma samples containing drugs with internal standard were reacted with non-labeled propylchloroformate to derivatize tazobactam-M-1 and ceftolozane. Excess reagent was removed by quenching with benzylamine and employing solvent extract. The final extract was analyzed by LC/MS-MS. | 20 µL plasma sample + 20 µL working internal standard solution or 20 µL dilution solvent + 0.15 mL precipitation solvent to diluent with 150 µL of water (ceftolozane and tazobactam) or 750 µL of ammonium formate (tazobactam M-1) |
| **Internal standard** | Sulbactam, $d_7$-labeled propylchloroformate derivatives of tazobactam M-1 and ceftolozane | $[^{15}N_2, D_4]$MK-7625, $[^{13}C_2, ^{15}N_3]$-Tazobactam, $[^{13}C_2, ^{15}N_3]$-Tazobactam M1 |
| **Calibration standard Range (µg/mL)** | Range consisted of 10 concentrations/drug:<br>TOL:0.25 to 150.0 µg/mL<br>TAZ: 0.1 to 60.0 µg/mL<br>TAZ-M-1: 0.05 to 30 µg/mL | Range consisted of 8 concentrations/drug:<br>TOL:0.25 to 150 µg/mL<br>TAZ: 0.1 to 60 µg/mL<br>TAZ-M-1: 0.05 to 30 µg/mL |
| **Inter-day Accuracy (RE%)** | TOL: -2.0 to 2.4<br>TAZ: -6.3 to 6.8<br>TAZ-M-1: -1.2 to 2.0 | TOL: -5.3 to 4.0<br>TAZ: -1.7 to 1.3<br>TAZ-M-1: 4.3 to 5.0 |
| **QC Levels (µg/mL)** | TOL:0.25, 0.75, 10, 120 µg/mL<br>TAZ: 0.1, 0.3, 4, 48 µg/mL<br>TAZ-M-1: 0.05, 0.15, 2, 24 µg/mL | TOL:0.25, 0.75, 11.3, 113 µg/mL<br>TAZ: 0.3, 4.5, 45 µg/mL<br>TAZ-M-1: 0.15, 2.25, 22.5 µg/mL |
| **Highest Dilution QC** | TOL: 300 µg/mL<br>TAZ: 120 µg/mL<br>TAZ-M-1: 60 µg/mL | TOL: 226 µg/mL<br>TAZ: 90 µg/mL<br>TAZ-M-1:45 µg/mL |
| **Inter-day Accuracy (RE%)** | TOL:0.83 to 3.3<br>TAZ: 0.0 to 2.8<br>TAZ-M-1: -0.8 to 2.7 | TOL: -2.7 to 3.5<br>TAZ: -2.3 to 2.0<br>TAZ-M-1: -1.8 to 4.4 |
| **Inter-day Precision (%CV)** | TOL: 5.0 to 7.2<br>TAZ: 5.4 to 9.6<br>TAZ-M-1: 6.0 to 7.3 | TOL: 5.1 to 12.2<br>TAZ: 3.8 to 12.5<br>TAZ-M-1: 3.0 to 6.2 |
| **Intra-day Accuracy (RE%)** | TOL: -6.7 to 8.8<br>TAZ: -12 to 10<br>TAZ-M-1: 8.5 to 11.3 | TOL: -10.7 to 13.3<br>TAZ: -11.7 to 6.3<br>TAZ-M-1: -5.6 to 10.7 |
| **Intra-day Precision (%CV)** | TOL: 1.0 to 13.3<br>TAZ: 1.3 to 16.3<br>TAZ-M-1: 0.9 to 10.3 | TOL: 1.9 to 13.4<br>TAZ: 6.7 to 12.3<br>TAZ-M-1: 0.9 to 5.1 |
| **Storage Stability** | 286 days at -70°C<br>4 cycles freeze thaw (-70°C to On Ice)<br>6 hours at room temp<br>39 days 5°C (working standard)<br>46 to 47 hours at 5°C (Processed sample) | 832 days at -80°±15°C (TOL and TAZ); 663 days at -80°±15°C (TAZ-M-1)<br>3 cycles freeze thaw from -80°C to room temp<br>5.5 hrs at room temp (bench top) and 5°C (short term)<br>22.3 hrs in ice-water bath (bench top)<br>120 hr at 5°C (autosampler)<br>1.5 and 3 hrs at room temp and ice (human blood) |

*Source: Collated by the Reviewer*

**Table 15-11: Bioanalytical Method Performance Summary**

| Study number | MK-7625A-010, PF14B-0167 | 2018-4485 (MK-77625A-034) | 2018-4486 (MK-7625A-035-02) |
|---|---|---|---|
| **Method of Detection** | LC-MS/MS | LC-MS/MS | LC-MS/MS |
| **Samples Received** | A total of 166 of the 322 samples received were analyzed. CRO notes that only the 166 samples were unique. The storage temperature was -70°C. | A total of 351 of the 353 samples received were analyzed. The storage temperature was -80°C. | A total of 265 of the 265 samples received were analyzed. Also, 3 samples from study protocol # 2018-4485 were received. The storage temp was -80°C |
| **Method reproducibility Incurred Sample Re-analysis (ISR)** | ISR findings showed the following drugs from 16 samples (total 166 samples) had a passing rate: TOL at 100%, TAZ 100%, and TAZ-M-1 at 75% (12 of 16 samples). | ISR findings showed the following drugs from 40 samples (total 351 samples) had passing rate: TOL at 100%, TAZ at 92.5%, and TAZ-M-1 at 100%. | ISR findings showed the following drugs from 27 samples (total 265 samples) had passing rate: TOL at 100%, TAZ at 92.6%, and TAZ-M-1 at 92.6%. |
| **Calibration standard Inter-day Accuracy (RE%)**<br>TOL(0.25 to 150 µg/mL)<br>TAZ (0.1 to 60 µg/mL)<br>TAZ-M-1 (0.05 to 30 µg/mL) | TOL: -1.0 to 1.0<br>TAZ: -2.4 to 4.5<br>TAZ-M-1: -2.6 to 2.4 | TOL: -6.7 to 3.6<br>TAZ:-2.5 to 2.0<br>TAZ- M-1:-3.3 to 2.4 | TOL: -2.7 to 2.4<br>TAZ: -2.8 to 4.5<br>TAZ-M-1: -4.6 to 3.7 |
| **QC Levels (µg/mL)** | TOL:0.75, 10, 120 µg/mL<br>TAZ: 0.3, 4, 48 µg/mL<br>TAZ-M-1: 0.15, 2, 24 µg/mL | TOL:0.75, 11.3, 113 µg/mL<br>TAZ: 0.3, 4.5, 45 µg/mL<br>TAZ-M-1: 0.15, 2.25, 22.5 µg/mL | |
| **QC Inter-day Accuracy (RE%)** | TOL: -0.8 to 1.5<br>TAZ: -2.0 to 1.0<br>TAZ-M-1: -1.7 to 2.0 | TOL: -2.7 to 2.9<br>TAZ: -2.0 to 0.7<br>TAZ-M-1: -1.8 to 2.7 | TOL: -2.7 to 4.0<br>TAZ: -2.0 to 3.6<br>TAZ-M-1: -0.9 to 2.7 |
| **QC Inter-day Precision (%CV)** | TOL: 7.2 to 8.3<br>TAZ: 6.5 to 8.3<br>TAZ-M-1: 5.7 to 7.2 | TOL: 4.3 to 7.4<br>TAZ: 4.6 to 9.6<br>TAZ-M-1: 3.7 to 4.0 | TOL: 4.7 to 5.5<br>TAZ: 6.8 to 9.0<br>TAZ-M-1: 4.5 to 6.8 |

*Source: Collated by the Reviewer*

## 15.2.3. Pharmacometrics

### 1. Population PK analysis

### 1.1 Review Summary

The Applicant's population pharmacokinetics (PPK) analysis for Ceftolozane/Tazobactam is acceptable to support the current submission as outlined in Table 15-12. The Applicant's final PPK model adequately described the observed Ceftolozane/Tazobactam plasma concentrations. Parameter estimates for the final model were estimated with acceptable precision with relative standard error (RSE) (<5%) for total clearance (CL) and volume of distribution in central compartment (V1), and the shrinkages for inter-individual variability on CL and V1 were less than 30%. The goodness-of-fit plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time or predicted concentrations. The visual predictive check (VPC) plots showed a good agreement between the

observed and the simulated concentrations. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

Ceftolozane/Tazobactam is substantially excreted by the kidney. The updated PPK model identified renal maturation as the most significant covariate on the pediatric PK of Ceftolozane/ Tazobactam. Per the current approved labeling, dose adjustments are recommended for pediatrics (birth to less 18 years of age with eGFR >50 mL/min/1.73 $m^2$) as following.

- cIAI pediatrics, 30 mg/kg (b) (4) up to a maximum dose of 1.5 g (b) (4) every 8 hours with 5-14 days treatment.
- cUTI and pyelonephritis pediatrics, 30 mg/kg (b) (4) up to a maximum dose of 1.5 g (b) (4) every 8 hours with 7-14 days treatment.

**Table 15-12: Specific Comments on Applicant's Final Population PK model**

| **Utility of the final model** | | | **Reviewer's Comments** |
|---|---|---|---|
| **Support applicant's proposed labeling statements about intrinsic and extrinsic factors** | **Intrinsic factor** | Based on the PPK analysis, renal maturation, infection type (cUTI, cIAI) and eGFR have statistically significant effects on CL and V1 with fixed allometric effects of body weight on CL, clearance in peripheral compartment (Q) , V1 and volume of distribution in peripheral compartment (V2). Additionally, the PPK model was used to estimate pediatric exposure and assess PTA, which were utilized to support Applicant's proposed following pediatric dosage:<br>• cIAI pediatrics, 30 mg/kg (b) (4) up to a maximum dose of 1.5 g (b) (4) every 8 hours with 5-14 days treatment.<br>• cUTI and pyelonephritis pediatrics, 30 mg/kg (b) (4) | The applicant adequately performed covariate assessment and evaluated the impact of potential covariates on ceftolozane PK following forward inclusion and backward elimination. Based on the estimated impact on ceftolozane exposure, the Reviewer agrees with the Applicant's conclusions. Inclusion of covariates into the base model were determined with the significance level of 0.01 based on $\chi 2$ test ($p < 0.01$, a decrease in OBJ > 6.63 for one degree of freedom).<br>In the stepwise backward deletion, deletion of covariates from the full model was determined with the significance level of 0.001 based on $\chi 2$ test ($p < 0.001$, an increase in OBJ > 10.84 for one degree of freedom or an increase in OBJ > 13.82 for two degrees of freedom) to construct a final model.<br>Additionally, the Applicant's PPK model is acceptable for pediatric dose selection via pharmacokinetic simulation. |

| | | | |
|---|---|---|---|
| | | [redacted](b) (4) up to a maximum dose of 1.5 g [redacted](b) (4) every 8 hours with 7-14 days treatment. | |
| | **Extrinsic factor** | NA | NA |
| **Derive exposure metrics for Exposure-response analyses** | Cmax, Cmin, AUCss | | The Applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (**Table 5**). |
| **Predict exposures at alternative dosing regimen** | NA | | NA |

*NA:* Not Available.

### 1.2 Introduction

The primary objectives of Applicant's analysis were to:

- Characterize the structural pharmacokinetic (PK) model and quantify the pediatric population variability in the PK parameters of Ceftolozane/Tazobactam in pediatrics.
- Describe the effects of intrinsic and/or extrinsic factors on Ceftolozane/Tazobactam exposure.
- Generate individual clearance estimates for pediatrics that can be used for subsequent exposure-response analyses
- Justify the proposed dosage for pediatrics

### 1.3 Model development

Data

PPK models were developed by applicant to describe the PK of Ceftolozane/Tazobactam (CXA-201 or TOL/TAZ) pediatric data from two phase 2 studies MK-7625A-034 (P034) and MK-7625A-035 (P035), and one phase 1 study CXA-PEDS-13-08 (P010), shown in Table 15-13. P010 was conducted in patients with proven or suspected gram-negative infections, whereas P034 and P035 were conducted in patients with Complicated Urinary Tract Infection (cUTI) or Complicated Intra-Abdominal Infection (cIAI), respectively. For P010, 6 PK samples per participants were collected in group 1 to group 4 and sparse PK samples (3 samples per participants) were collected in group 5 and group 6. Only sparse PK samples were collected (3 samples per participants) in P034 and P035.

A total of 194 subjects from the three clinical studies were included in the analysis dataset, and 3 subjects were excluded due to unreasonable PK profiles. A total of 191 subjects were included in the final dataset: 35 (18.3%) from PN010, 89 (46.6%) from PN034, and 65 (35.1%) from PN035. There were 596 ceftolozane and 594 tazobactam samples in total in which, 2 samples were BLQ for ceftolozane and 98 samples BLQ for tazobactam. Data disposition for ceftolozane and tazobactam is summarized in Table 15-14. Characteristics of participants in all three studies, including covariates of interest, are summarized in Table 15-15.

**Table 15-13: Summary of Designs of Studies Included in the Population PK Analyses**

| Study | Number of subjects | Population | Dosing regimen | PK measurements |
|---|---|---|---|---|
| CXA-PEDS-13-08 (P010) | 35 | Pediatric patients receiving standard of care antibiotic therapy for proven or suspected gram-negative infection or for perioperative prophylaxis<br><br>Group 1 :12 to <18 years<br>Group 2: 7 to < 12 years<br>Group 3: 2 to < 7 years<br>Group 4: 3 months to < 2 years<br>Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months*<br>Group 6 birth [≤ 32 weeks gestation, 7 days postnatal] to < 3 months* | C/T administered as 1-hour infusion every 8 hours.<br><br>Group 1 (n = 6): 1.5g C/T<br>Group 2 (n = 6): 27 mg/kg C/T<br>Group 3 (n = 6,): 27 mg/kg CT; and 45 mg/kg C/T<br>Group 4 (n = 6): 27 mg/kg C/T; and 45 mg/kg C/T<br>Group 5 (n = 6): 30 mg/kg C/T<br>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 $m^2$) | For Groups 1 - 4, plasma samples were collected at 0, 0.5 (optional), 1, 2, 4, and 6 hours after start of infusion<br>For Groups 5 - 6, plasma samples were collected at 1, 2, and 6 hours after start of infusion |
| MK-7625A-034 | 133 | Pediatric subjects with cUTI, including pyelonephritis<br><br>Group 1 :12 to <18 years<br>Group 2: 7 to < 12 years<br>Group 3: 2 to < 7 years<br>Group 4: 3 months to < 2 years<br>Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months* | C/T administered as 1-hour infusion every 8 hours.<br>Group 1 (n = 20, 50 in combination with Group 2): 3:1 randomization to 1.5g C/T or 20 mg meropenem<br>Group 2 (n = 32, 50 in combination with Group 2): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem<br>Group 3 (n = 29): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem<br>Group 4 (n = 31): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem<br>Group 5 (n = 21): 3:1 randomization to 30 mg/kg C/T or 20 mg meropenem | After administration of at least 6 doses. Plasma samples were collected at end of infusion, between 3-4 hours and 6-7 hours (pre-next dose) after end of infusion |
| MK-7625A-035 | 91 | Pediatric subjects with cIAI, including pyelonephritis<br><br>Group 1 :12 to <18 years<br>Group 2: 7 to < 12 years<br>Group 3: 2 to < 7 years<br>Group 4: 3 months to < 2 years<br>Group 5: birth [> 32 weeks gestation, 7 days postnatal] to < 3 months* | C/T administered as 1-hour infusion every 8 hours.<br>Group 1 (n = 21, 50 in combination with Group 2): 3:1 randomization to 1.5g C/T + 10 mg/kg metronidazole or 20 mg meropenem<br>Group 2 (n = 39, 50 in combination with Group 2): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem<br>Group 3 (n = 29): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem<br>Group 4 (n = 1): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem<br>Group 5 (n = 1): 3:1 randomization to 30 mg/kg C/T + 10 mg/kg metronidazole to 20 mg meropenem | After administration of at least 6 doses. Plasma samples were collected at end of infusion, between 3-4 hours and 6-7 hours (pre-next dose) after end of infusion |
| *Age definition per individual protocol | | | | |

*Source: Applicant's 05qwch, Table 1 on Page 28 (link).*

**Table 15-14: Summary of Ceftolozane and Tazobactam Pharmacokinetic Data Disposition for Pediatric Studies Included in the Modeling Dataset**

| Description | MK-7625A-010 | MK-7625A-034 | MK-7625A-035 | Total |
|---|---|---|---|---|
| Ceftolozane | | | | |
| Number of observations | 135 | 258 | 201 | 594 |
| Number of BLQ samples | 0 | 2 | 0 | 2 |
| Number of excluded samples | 0 | 6 | 3 | 9 |
| Number of doses | 35 | 1493 | 1326 | 2854 |
| Number of excluded doses | 0 | 28 | 18 | 46 |
| Total | 170 | 1787 | 1548 | 3505 |
| Tazobactam | | | | |
| Number of observations | 115 | 211 | 169 | 495 |
| Number of BLQ samples | 18 | 49 | 32 | 99 |
| Number of excluded samples | 0 | 6 | 3 | 9 |
| Number of doses | 35 | 1493 | 1326 | 2854 |
| Number of excluded doses | 0 | 28 | 18 | 46 |
| Total | 168 | 1787 | 1548 | 3503 |

*Source: Applicant's 05qwch, Table 1 on Page 41 (link).*

**Table 15-15: Summary of Characteristics of Participants in Pediatric Studies Included in the Modeling Dataset**

| | Overall, n = 191 [a] | Group 1 (12y, 18y), n = 36[a] | Group 2 (7y, 12y), n= 48 [a] | Group 3 (2y, 7y), n= 53 [a] | Group 4 (3m, 2y), n = 28 [a] | Group 5 (birth, 3m), n = 21 [b] | Group 6 (0, 3m), n = 5 [c] |
|---|---|---|---|---|---|---|---|
| **STUDY** | | | | | | | |
| MK-7625A-010 | 35 (18%) | 6 (17%) | 6 (12%) | 6 (11%) | 6 (21%) | 6 (29%) | 5 (100%) |
| MK-7625A-034 | 89 (47%) | 14 (39%) | 15 (31%) | 24 (45%) | 22 (79%) | 14 (67%) | 0 (0%) |
| MK-7625A-035 | 67 (35%) | 16 (44%) | 27 (56%) | 23 (43%) | 0 (0%) | 1 (4.8%) | 0 (0%) |
| **AGE (Years)** | 6.3 (5.3)<br>0.0 -- 17.5 | 14.8 (1.7)<br>12.0 -- 17.5 | 8.8 (1.4)<br>7.0 -- 11.0 | 4.0 (1.4)<br>2.0 -- 6.6 | 0.9 (0.4)<br>0.2 -- 1.7 | 0.1 (0.0)<br>0.0 -- 0.2 | 0.1 (0.1)<br>0.1 -- 0.2 |
| **SEX** | | | | | | | |
| Female | 95 (50%) | 18 (50%) | 25 (52%) | 31 (58%) | 14 (50%) | 4 (19%) | 3 (60%) |
| Male | 96 (50%) | 18 (50%) | 23 (48%) | 22 (42%) | 14 (50%) | 17 (81%) | 2 (40%) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **WEIGHT (Kg)** | 25.3(19.1)<br>1.1 -- 90.0 | 55.2 (13.2)<br>33.0 -- 90.0 | 32.8 (9.9)<br>19.8 -- 75.3 | 17.5 (4.8)<br>11.8 -- 36.0 | 8.6 (1.8)<br>5.2 -- 11.9 | 4.4 (1.0)<br>2.6 -- 6.2 | 2.2 (1.0)<br>1.1 -- 3.7 |
| **eGFR (mL/min/1.73 $m^2$)** | 147.6(65.3)<br>30.2 -- 561.0 | 155.6 (59.6)<br>46.2 -- 366.3 | 165.0 (41.1)<br>86.3 -- 293.7 | 163.6 (77.6)<br>75.4 -- 561.0 | 138.1 (68.1)<br>55.0 -- 427.8 | 83.8 (28.0)<br>55.8 -- 139.5 | 73.8 (37.8)<br>30.2 -- 113.7 |
| **RACE** | | | | | | | |
| Asian | 3 (1.6%) | 0 (0%) | 0 (0%) | 2 (3.8%) | 1 (3.6%) | 0 (0%) | 0 (0%) |
| Black | 12 (6.3%) | 2 (5.6%) | 4 (8.3%) | 1 (1.9%) | 0 (0%) | 1 (4.8%) | 4 (80%) |
| Other | 5 (2.6%) | 0 (0%) | 1 (2.1%) | 1 (1.9%) | 2 (7.1%) | 0 (0%) | 1 (20%) |
| White | 171 (90%) | 34 (94%) | 43 (90%) | 49 (92%) | 25 (89%) | 20 (95%) | 0 (0%) |
| **INFECTION TYPE** | | | | | | | |
| cIAI | 67 (35%) | 16 (44%) | 27 (56%) | 23 (43%) | 0 (0%) | 1 (4.8%) | 0 (0%) |
| cUTI | 89 (47%) | 14 (39%) | 15 (31%) | 24 (45%) | 22 (79%) | 14 (67%) | 0 (0%) |
| Other | 35 (18%) | 6 (17%) | 6 (12%) | 6 (11%) | 6 (21%) | 6 (29%) | 5 (100%) |
| Pyelonephritis | 75 (39%) | 14 (39%) | 9 (19%) | 19 (36%) | 18 (64%) | 15 (71%) | 0 (0%) |
| Appendicitis | 66 (35%) | 14 (39%) | 27 (56%) | 25 (47%) | 0 (0%) | 0 (0%) | 0 (0%) |

[a]Statistics presented: n (%); Mean (SD); Minimum – Maximum

b: birth [> 32 weeks gestation, 7days postnatal] to < 3 months

c: birth [≤ 32 weeks gestation, 7 days postnatal] to < 3 months ;

*Source: adapted from Applicant's 05qwch, Table 3 on Page 42 (link).*

**Base model**

The base model was a two-compartment PK model with infusion and first-order elimination from the central compartment using informative priors from the adult nosocomial pneumonia (NP) model[17], in which fixed allometric functions of body weight for clearance (CL, Q) and volume parameters (V1 and V2) was included, as appropriate. This model was reviewed previously in the Supplement 8 Unireview in DARRTs on 5/31/2019.

Inter-individual variability was modelled assuming a log-normal distribution for patient level random effects. The inter-individual variability was considered for CL and V1.

Intra-individual variability was tested as combination error model (the additive error + the proportional error model) on the dependent variable.

Model evaluation and selection utilized the Bayesian approach and prior information from previous adult NP model, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV) and successful model convergence.

**Covariate analysis**

Covariate parameters, including renal maturation, estimated glomerular filtration rate (eGFR), body weight, age, sex, race, and infection were tested on ceftolozane PK.

Covariates (power model, piece-wise linear model, power + linear combination model and multiplicative model) were assessed for covariates with forward selection criteria of the significant level of 0.01 based on $\chi 2$ test ($p < 0.01$, a decrease in OBJ > 6.63 for one degree of freedom) and backward deletion criteria with the significance level of 0.01 based on $\chi 2$ test ($p < 0.001$, an increase in OBJ > 10.84 for one degree of freedom and an increase in OBJ > 13.82 for two degrees of freedom).

**Final Model**

The parameter estimates for the final PPK model are listed in Table 15-16. Posterior parameter distributions are shown in **Figure 6** and **Figure 10**. The goodness-of-fit plots for the final covariate model are shown in **Figure 7** and **Figure 11**. Overall, VPC and VPC by age categories were shown in **Figure 8**, **Figure 9**, **Figure 12**, and **Figure 13**. The structural model for the final PPK model was a 2-compartmental model as parameterized with CL, V1, V2, and Q2 for Ceftolozane and Tazobactam with fixed-exponent allometric scaling of weight on central and intercompartmental clearance as well as volume (central and peripheral). An exponential error model was used for inter-individual variability, and proportional error model was used for intra-individual variability.

[17] Darrts: Wang, Deborah REV-summary-13 (Unireview) Supplement-8 (Efficacy) 05/31/2019

**Table 15-16: Population Pharmacokinetic Parameter Estimates for the Final Model**

Final Population PK Parameter Estimates: Ceftolozane (run1016)

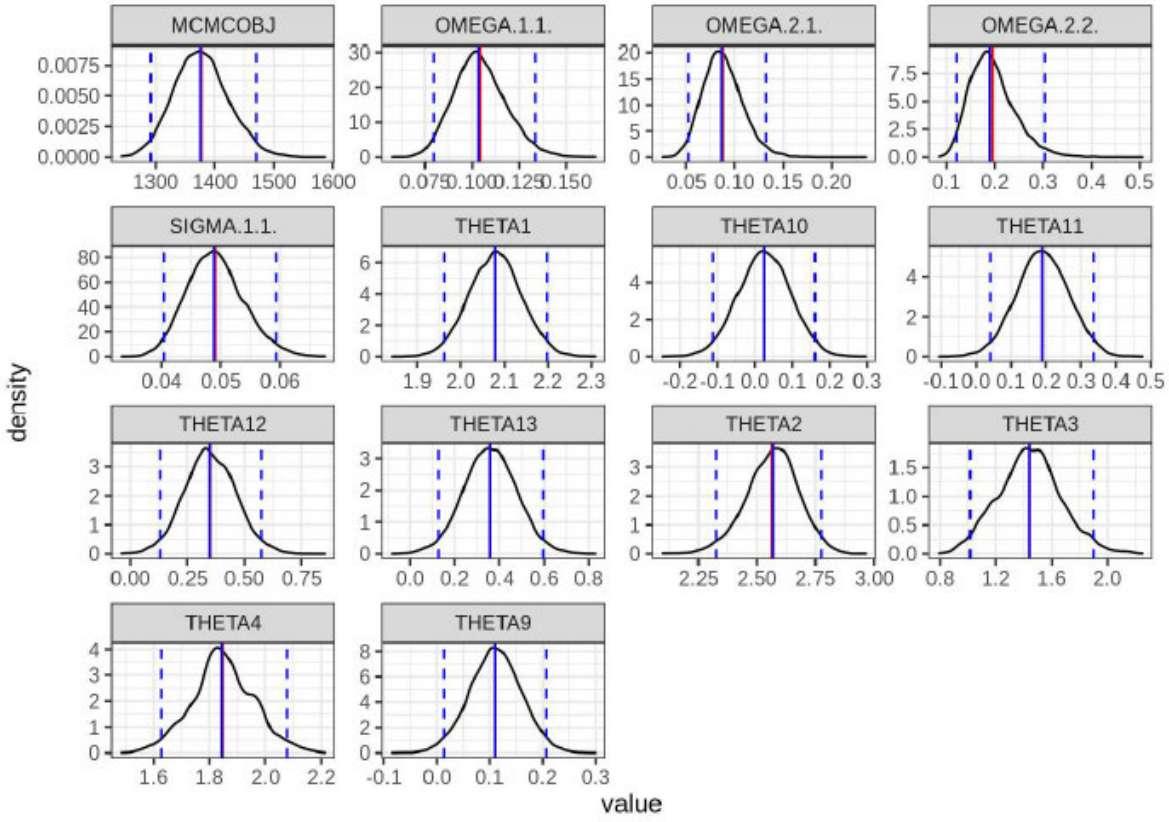
| Parameters | Fixed effect (%RSE) | IIV %CV (%RSE) |
|---|---|---|
| **CL (L/h): Systemic Clearance** | 8 (2.88) | 33.2 (13.3) |
| **~eGFR [power model]** | 0.11 (44) | – |
| **~Infection (cUTI)** | 1.03 (269) | – |
| **~Infection (cIAI)** | 1.21 (39.3) | – |
| **V1 (L): Central Volume** | 13 (4.4) | 46.4 (24) |
| **~Infection (cUTI)** | 1.42 (32.1) | – |
| **~Infection (cIAI)** | 1.43 (33.1) | |
| **V2 (L): Peripheral Volume** | 4.23 (15.6) | |
| **Q (L/h): Intercompartmental Clearance** | 6.35 (6.01) | – |
| **Residual variability (%)** | 22.2 (9.74) | – |

Final Population PK Parameter Estimates: Tazobactam (run1010)

| Parameters | Fixed effect (%RSE) | IIV %CV (%RSE) |
|---|---|---|
| **CL (L/h)** | 17.7 (2.23) | 31.6 (17.6) |
| **~eGFR [power model]** | 0.36 (18.8) | – |
| **V1 (L)** | 13.5 (3.88) | 102 (26.1) |
| **V2 (L)** | 3.76 (3.91) | 21.9 (70.2) |
| **Q (L/h)** | 5.31 (2.21) | – |
| **Residual variability (%)** | 38.3 (9.85) | – |

*Source: Applicant's 05qwch, Table 3 on Page 18 (link).*

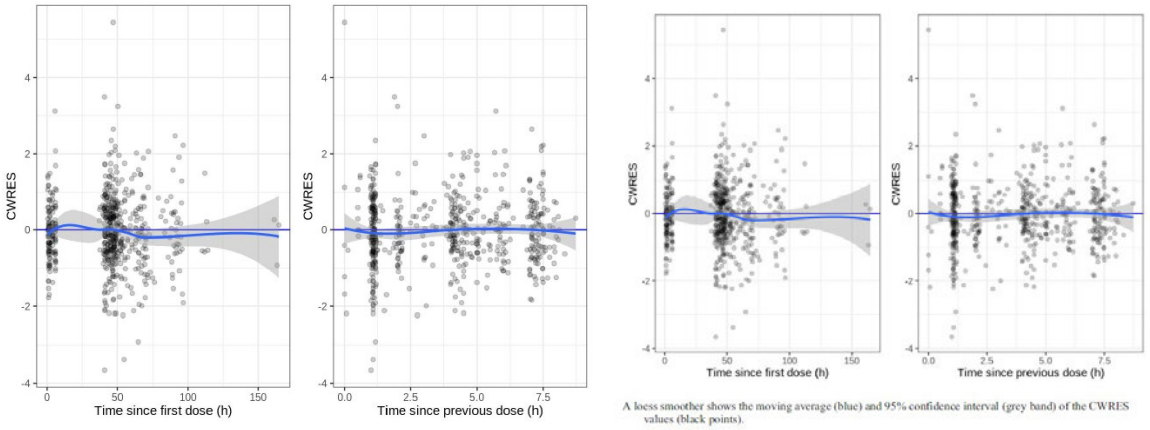
**Figure 6: Posterior Parameter Distributions of Ceftolozane Final Model**



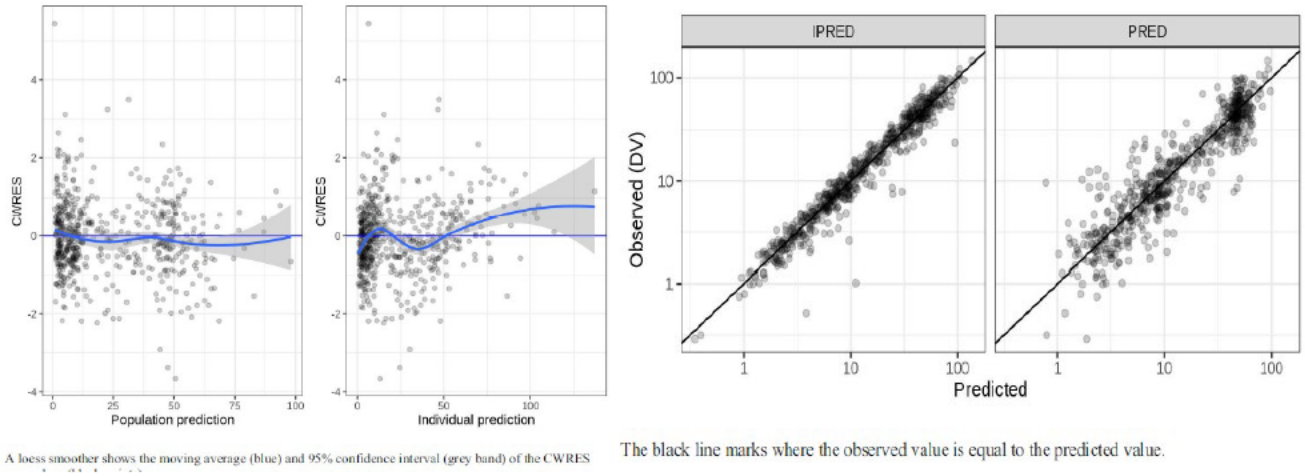

The black line indicates the probability density curve of the posterior. The solid blue line marks the median and the dashed blue lines mark the bounds of the 95% credibility interval (at the 2.5th and 97.5th percentiles). The solid red line marks the mean.

*Source: Applicant's 05qwch, Figure 5 on Page 52 (link).*

**Figure 7: Goodness of fit of Ceftolozane Final Model**

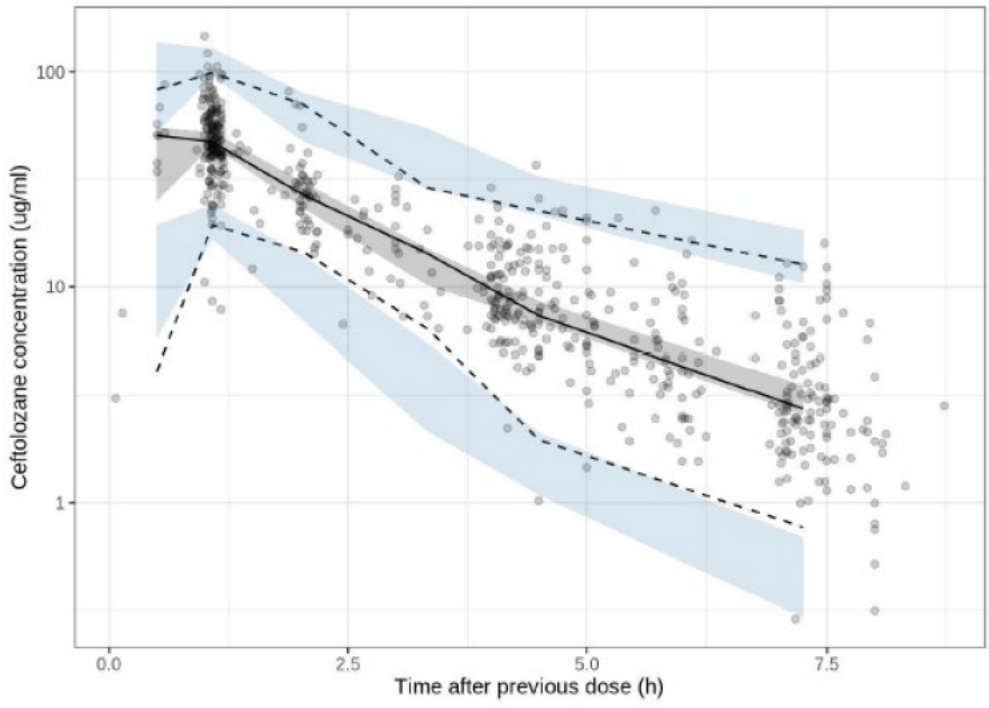



A loess smoother shows the moving average (blue) and 95% confidence interval (grey band) of the CWRES values (black points).




*Source: Applicant's 05qwch, Figure 7-9 on Page 54-57 (link).*

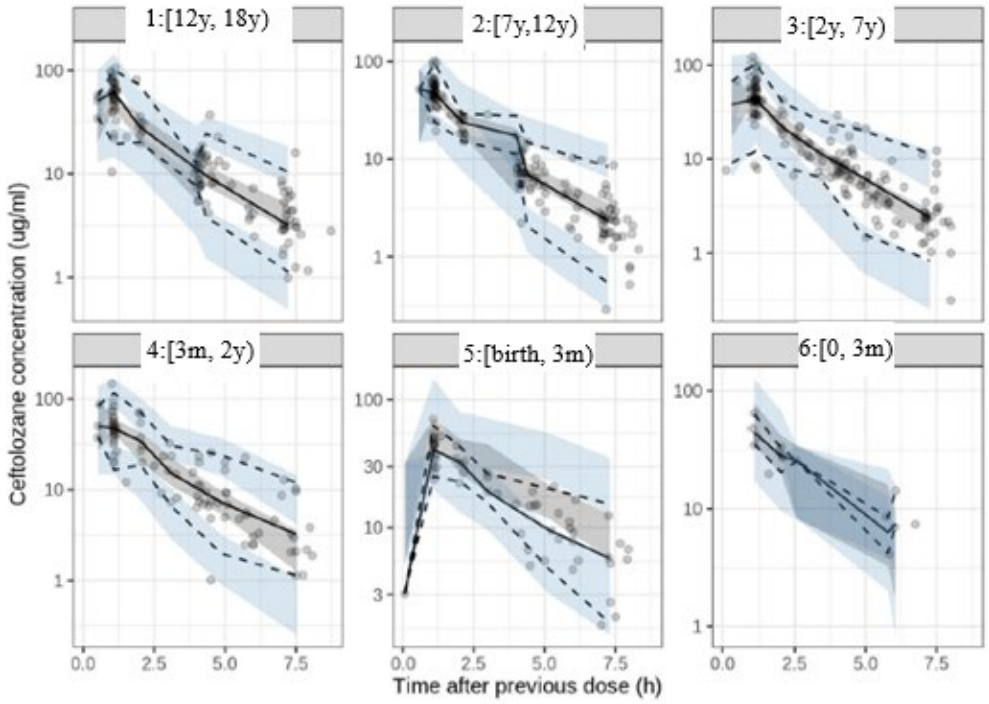
**Figure 8: Overall VPC for Ceftolozane Final Model**




The 5th and 95th percentiles of the data are shown by dashed lines, and the median by a solid line. The 95% CI of the predicted 5th and 95th percentiles are shown by blue bands, and the 95% CI of the median is shown by a gray band.

*Source: Applicant's 05qwch, Figure 10 on Page 58 (link).*

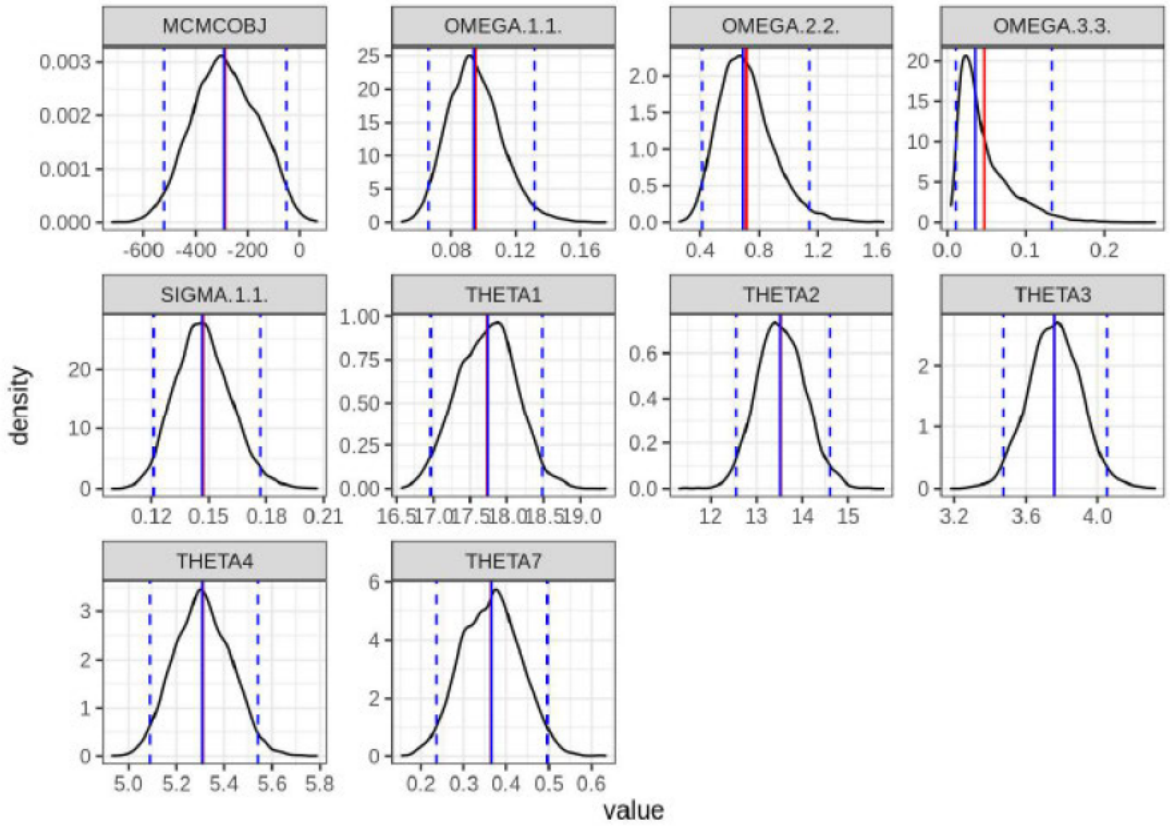
**Figure 9: VPC by Age Categories for Ceftolozane Final Model**




The 5th and 95th percentiles of the data are shown by dashed lines, and the median by a solid line. The 95% CI of the predicted 5th and 95th percentiles are shown by blue bands, and the 95% CI of the median is shown by a gray band.

*Source: Adapted from Applicant's 05qwch, Figure 11 on Page 59 (link).*

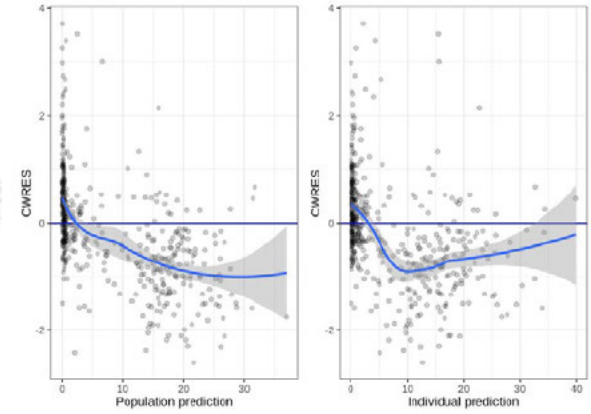
**Figure 10: Posterior Parameter Distributions of Tazobactam Final Model**




The black line indicates the probability density curve of the posterior. The solid blue line marks the median and the dashed blue lines mark the bounds of the 95% credibility interval (at the 2.5th and 97.5th percentiles). The solid red line marks the mean.

*Source: Applicant's 05qwch, Figure 18 on Page 69 (link).*

**Figure 11: Goodness of fit of Tazobactam Final Model**




A loess smoother shows the moving average (blue) and 95% confidence interval (grey band) of the CWRES values (black points).

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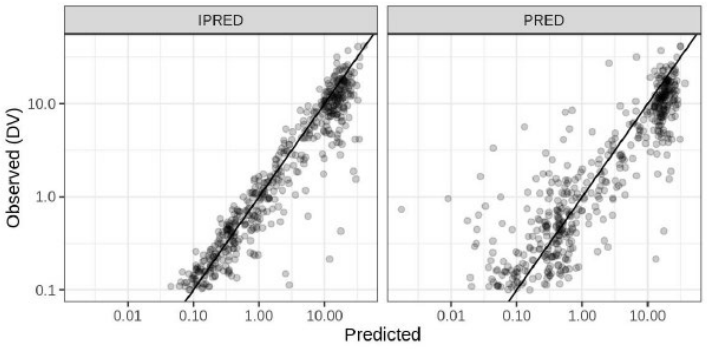
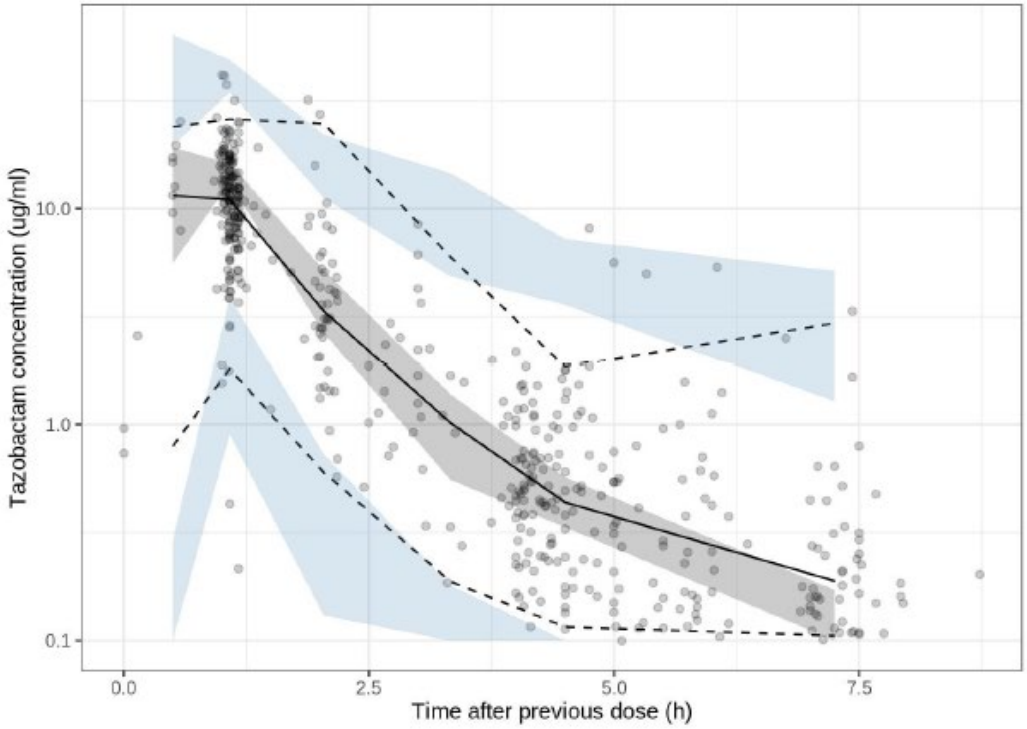



The black line marks where the observed value is equal to the predicted value.

*Source: Applicant's 05qwch, Figure 20-22 on Page 71-73 (link).*

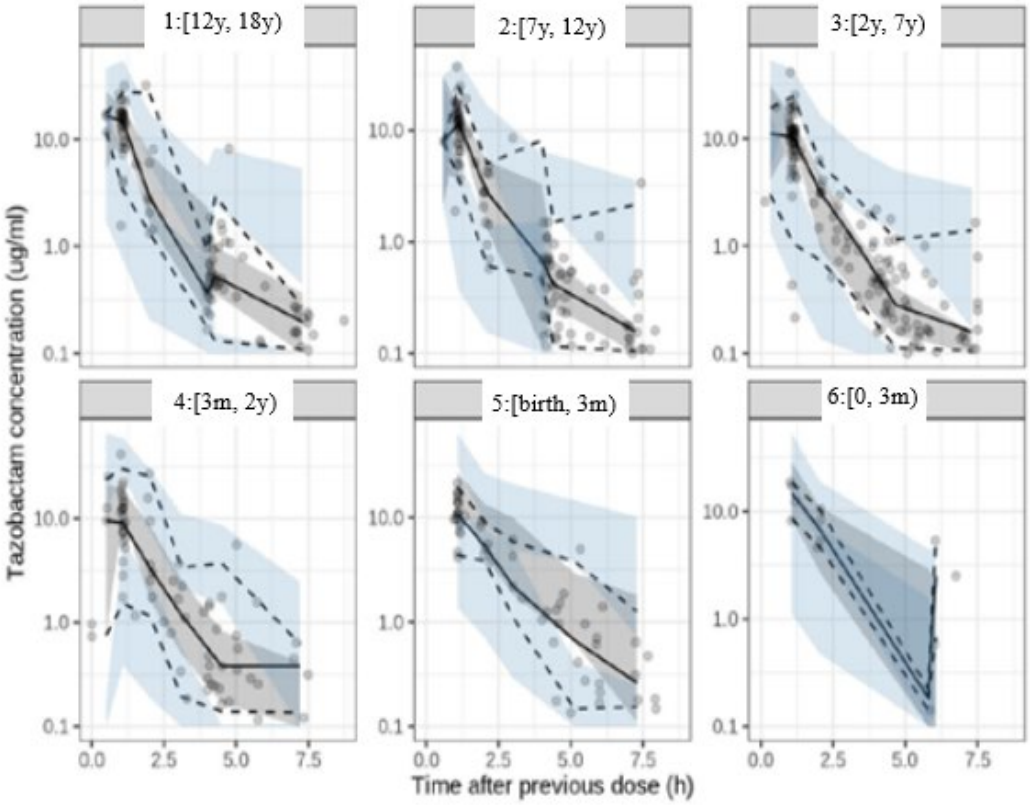
**Figure 12: Overall VPC for Tazobactam Final Model**




The 5th and 95th percentiles of the data are shown by dashed lines, and the median by a solid line. The 95% CI of the predicted 5th and 95th percentiles are shown by blue bands, and the 95% CI of the median is shown by a gray band.

*Source: Applicant's 05qwch, Figure 23 on Page 74 (link).*

**Figure 13: VPC by Age Category for Tazobactam Final Model**




The 5th and 95th percentiles of the data are shown by dashed lines, and the median by a solid line. The 95% CI of the predicted 5th and 95th percentiles are shown by blue bands, and the 95% CI of the median is shown by a gray band.

*Source: Adapted from Applicant's 05qwch, Figure 24 on Page 75 (link).*

### 1.5 Pediatric Bayesian Estimated Individual Exposures

Steady-state plasma PK parameters of ceftolozane and tazobactam estimated by PPK models in pediatric cUTI and cIAI patients across all age groups were estimated and summarized in Table 15-17 and Table 15-18.

**Table 15-17: Summary of Steady-State Ceftolozane and Tazobactam Plasma PK Parameter Values (GM and GCV%) Estimated by Population PK Model in Pediatric cUTI Participants in P034 Versus Adult (Phase 2/3) Studies**

| Parameters | Group 1 12 to <18 y n=14 | Group 2 7 to <12 y n=15 | Group 3 2 to <7 y n=24 | Group 4 3 mo to <2 y n=22 | Group 5 Birth to <3 mo n=14 | Adult cUTI patients n=156 |
|---|---|---|---|---|---|---|
| **Ceftolozane** | | | | | | |
| Ceftolozane / tazobactam dose | 1000/500 mg | 20/10 mg/kg | 20/10 mg/kg | 20/10 mg/kg | 20/10 mg/kg | 1000/500 mg |
| AUC0-8, µg*h/mL | 168 (35) | 137 (36) | 127 (37) | 119 (41) | 139 (29) | 203 (34) |
| $C_{eoi}$, µg/mL | 65.5 (34) | 58.5 (38) | 55.5 (40) | 46.9 (40) | 41.6 (28) | 70.6 (30) |
| t1/2, h | 2.26 (16) | 1.97 (22) | 1.8 (25) | 1.9 (34) | 2.58 (24) | 2.73 (29) |
| CL, L/h | 6 (35) | 4.7 (44) | 2.6 (40) | 1.4 (46) | 0.7 (48) | 4.92 (34) |
| Vss, L | 15 (33) | 10.4 (46) | 5.4 (41) | 3.2 (52) | 2.3 (44) | 16.1 (31) |
| **Tazobactam** | | | | | | |
| AUC0-8, µg*h/mL | 33.4 (33) | 26.3 (32) | 25.1 (28) | 26.5 (40) | 41.7 (41) | 31.3 (32) |
| $C_{eoi}$, µg/mL | 22 (29) | 19.3 (40) | 18.1 (31) | 17.2 (50) | 24.3 (39) | 19.9 (21) |
| t1/2, h | 1.26 (26) | 1.16 (29) | 1.02 (24) | 1.01 (37) | 1.08 (42) | 1.41 (19) |
| CL, L/h | 15 (32) | 12.3 (45) | 6.58 (42) | 3.15 (52) | 1.13 (61) | 16.0 (32) |
| Vss, L | 14.9 (40) | 8.33 (77) | 5.13 (59) | 2.79 (85) | 1.36 (55) | 18.6 (20) |

cUTI = Complicated urinary tract infection; AUC0-8=Area under the plasma concentration-time curve in the dosing interval 0 to 8 hours; $C_{eoi}$=Concentration at the end of infusion; CL= Clearance, t1/2= Terminal half-life; Vss = Volume of distribution at steady-state

*Source: adapted from Applicant's 05qwch, Table 7 on Page 80 (link).*

**Table 15-18: Summary of Steady-State Ceftolozane and Tazobactam Plasma PK Parameter Values (GM and GCV%) Estimated by Population PK Model in Pediatric cIAI Participants in P035 Versus Adult (Phase 2/3) Studies**

| Parameters | Group 1 12 to <18 y n=16 | Group 2 7 to <12 y n=27 | Group 3 2 to <7 y n=23 | Adult cIAI patients n=161 |
|---|---|---|---|---|

| Ceftolozane | | | | |
|---|---|---|---|---|
| Ceftolozane/ tazobactam dose | 1000/500 mg | 20/10 mg/kg | 20/10 mg/kg | 1000/500 mg |
| AUC0-8, µg*h/mL | 115 (43) | 113 (28) | 95.7 (27) | 148 (37) |
| $C_{eoi}$, µg/mL | 46.7 (50) | 51.2 (32) | 41.7 (34) | 53.8 (37) |
| t1/2, h | 2.12 (19) | 1.77 (13) | 1.69 (16) | 2.44 (27) |
| CL, L/h | 8.74 (43) | 5.53 (39) | 3.58 (33) | 6.75 (37) |
| Vss, L | 20.3 (51) | 10.7 (44) | 7.11 (37) | 19.6 (38) |
| **Tazobactam** | | | | |
| AUC0-8, µg*h/mL | 28.8 (46) | 29.5 (25) | 23.2 (28) | 27.6 (60) |
| $C_{eoi}$, µg/mL | 19.7 (48) | 20.3 (35) | 16.3 (41) | 15.4 (33) |
| t1/2, h | 1.24 (17) | 1.11 (14) | 0.991 (19) | 1.69 (40) |
| CL, L/h | 17.4 (46) | 10.6 (35) | 7.39 (35) | 18.1 (60) |
| Vss, L | 16.5 (56) | 9.46 (58) | 6.17 (64) | 26.6 (22) |

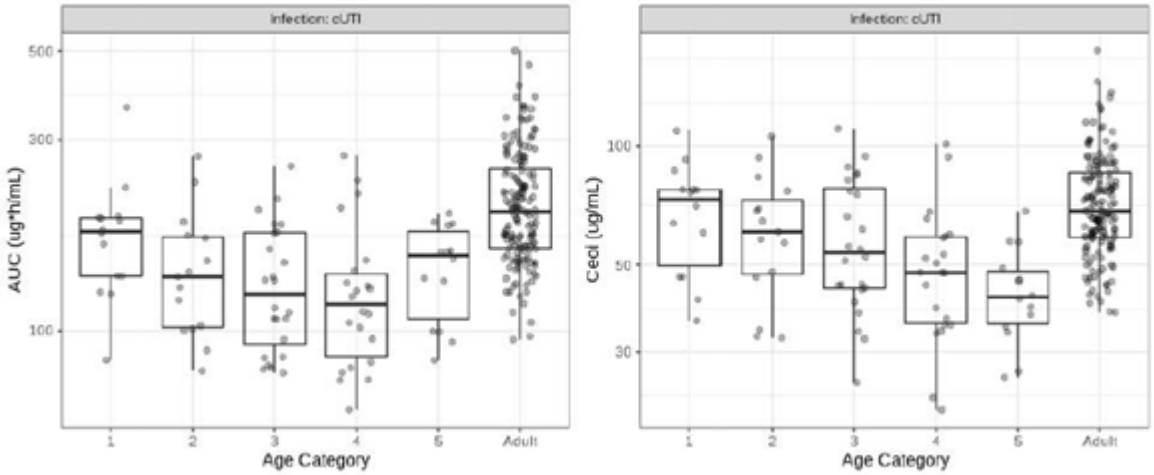
cIAI = Complicated intra-abdominal infection ; AUC0-8=Area under the plasma concentration-time curve in the dosing interval 0 to 8 hours; $C_{eoi}$=Concentration at the end of infusion; CL= Clearance, t1/2= Terminal half-life; Vss = Volume of distribution at steady-state

*One participant was enrolled in Group 4 in the C/T arm but discontinued before the day of PK sample collection; one participant was enrolled for Group 5 in the C/T arm with steady-state ceftolozane PK parameter values: AUC0-8=173 µg*h/mL; $C_{eoi}$=43.4 µg/mL; t1/2=3.29 h; CL=0.4 L/h; Vss=1.75 L; and with tazobactam PK parameter values: AUC0-8=69.9 µg*h/mL; $C_{eoi}$=30.5 µg/mL; t1/2=1.44 h; CL=0.5 L/h; Vss=0.95 L.

*Source: adapted from Applicant's 05qwch, Table 8 on Page 81 (link).*

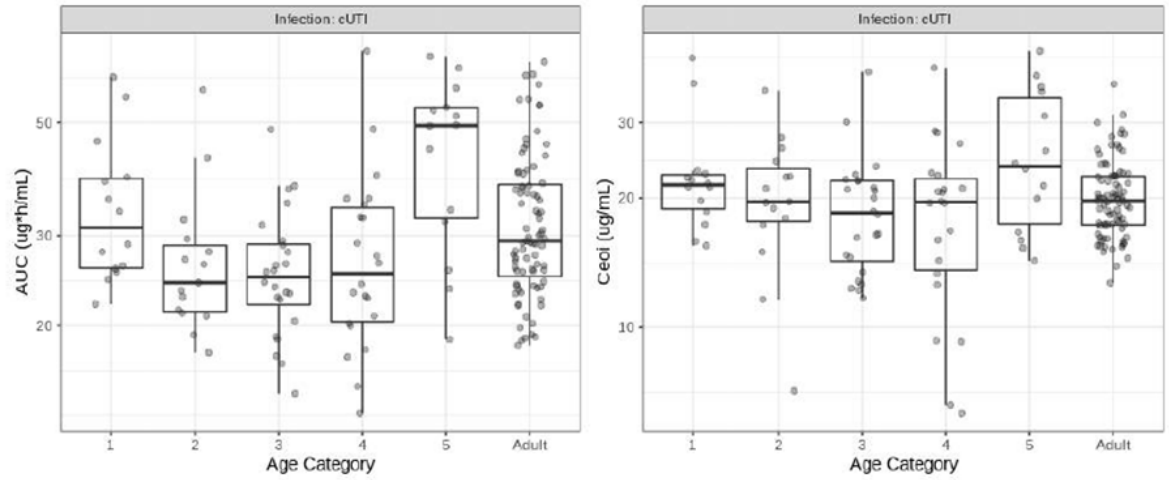
By comparison, the geometric means of AUC and Ceoi (Concentration after end of infusion) of ceftolozane in all pediatric age groups with cUTI or cIAI are lower than those of adults with cUTI or cIAI respectively. In addition, geometric mean of AUC of tazobactam in pediatric group 5 with cUTI is 33% higher than that in adult. The boxplots of AUC and Ceoi were substantial overlap in the exposure distributions between pediatric and adult participants with cUTI and cIAI, shown in **Figure 14**, **Figure 15**, **Figure 16**, and **Figure 17**.

**Figure 14: Comparison of Ceftolozane AUC0-8 and Ceoi in Participants with cUTI in the Pediatric (P034) Versus Adult (Phase 2/3) Studies**



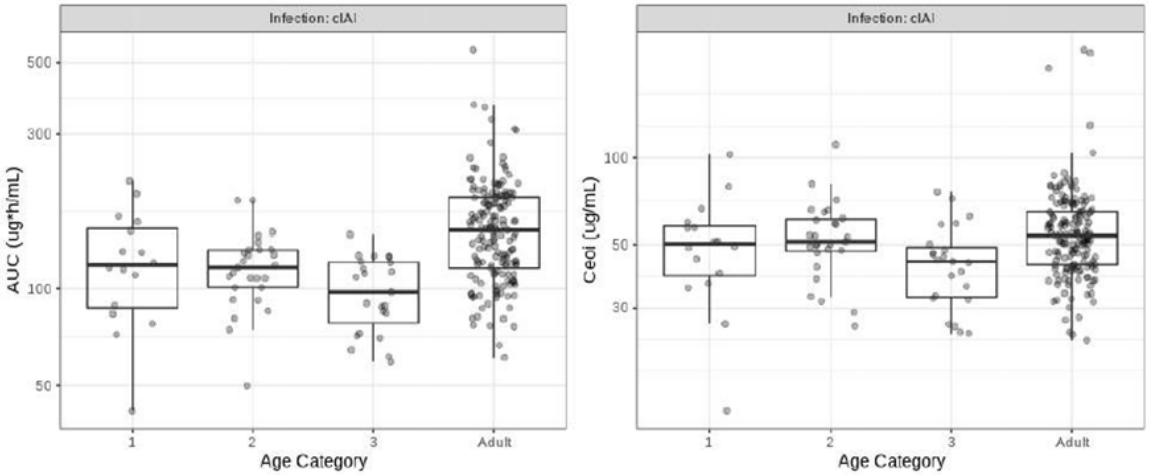

*Group 1: 12 to <18 years; Group 2: 7 to <12 years; Group 3: 2 to < 7 years; Group 4: 3 months to <2 years; Group 5: birth to < 3 months.*

**Figure 15: Comparison of Tazobactam AUC0-8 and Ceoi in cUTI Participants in the Pediatric (P034) Versus Adult (Phase 2/3) Studies**



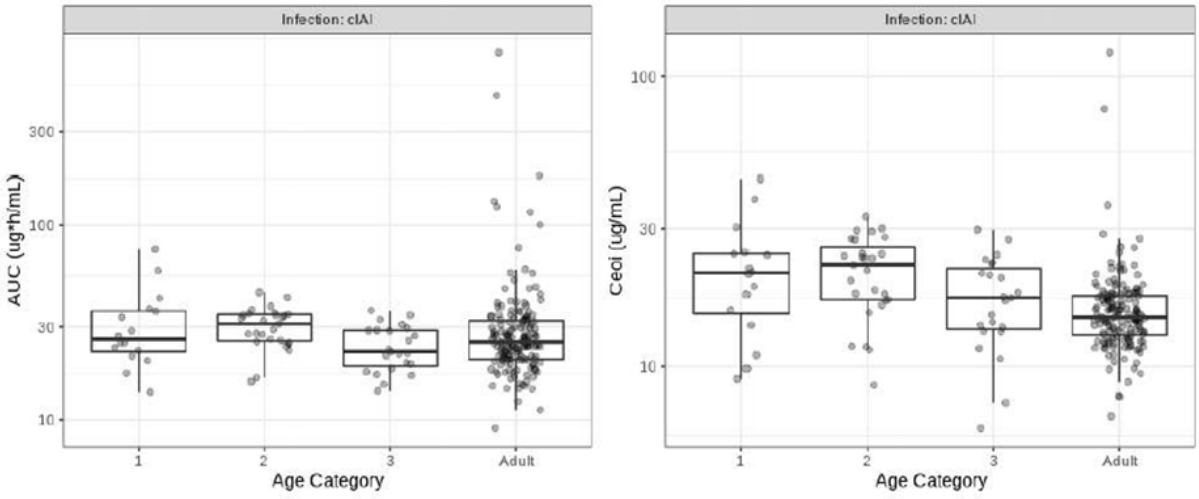

*Group 1: 12 to <18 years; Group 2: 7 to <12 years; Group 3: 2 to < 7 years; Group 4: 3 months to <2 years; Group 5: birth to < 3 months.*

**Figure 16: Comparison of Ceftolozane AUC0-8 and Ceoi in Participants with cIAI in the Pediatric (P035) Versus Adult (Phase 2/3) Studies**




*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.*

**Figure 17: Comparison of Tazobactam AUC0-8 and Ceoi in Participants with cIAI in the Pediatric (P035) Versus Adult (Phase 2/3) Studies**



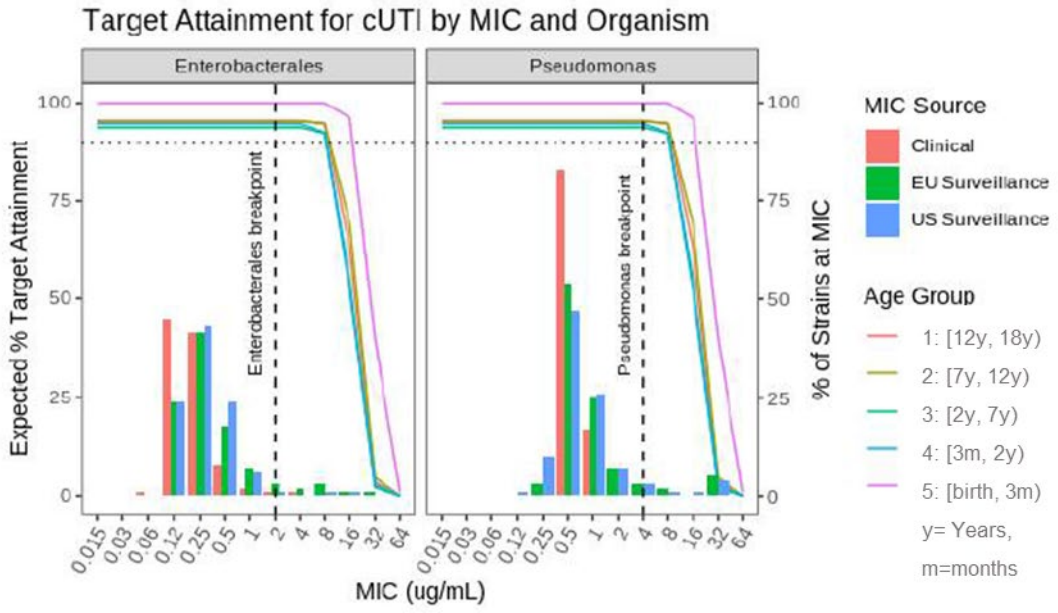

**Group 1: 12 to <18 years; Group 2: 7 to <12 years; Group 3: 2 to < 7 years; Group 4: 3 months to <2 years; Group 5: birth to < 3 months.**

*Source: Figures 14-18 adopted form Applicant's 05qwch, Table 10 on Page 82-83 (link).*

### 1.6 PTA assessment

Plasma joint probability of target attainment (PTA) assessments for ceftolozane and tazobactam in pediatric cUTI and cIAI patients were conducted by Monte Carlo simulations at the proposed dose. The simulations were used to elucidate a joint PTA at the relevant PK/PD targets for breakpoints of interest. For ceftolozane, a concentration that achieves >30% fraction of the dosing interval that plasma concentrations remain above the minimum inhibitory concentration (*f*T>MIC) is PK-PD target. For tazobactam, a concentration that achieves >20% fraction of the dosing interval that free plasma concentrations remain above a threshold concentration( *f*T>CT) of 1 µg/mL is PK-PD target. The percent of subjects who achieve >90% PTA at the PK/PD targets is reported as one of the final metrics of this analysis, to indicate appropriateness of the proposed dosing in pediatric patients with cUTI/cIAI, shown in **Figure 18** and **Figure 19**.

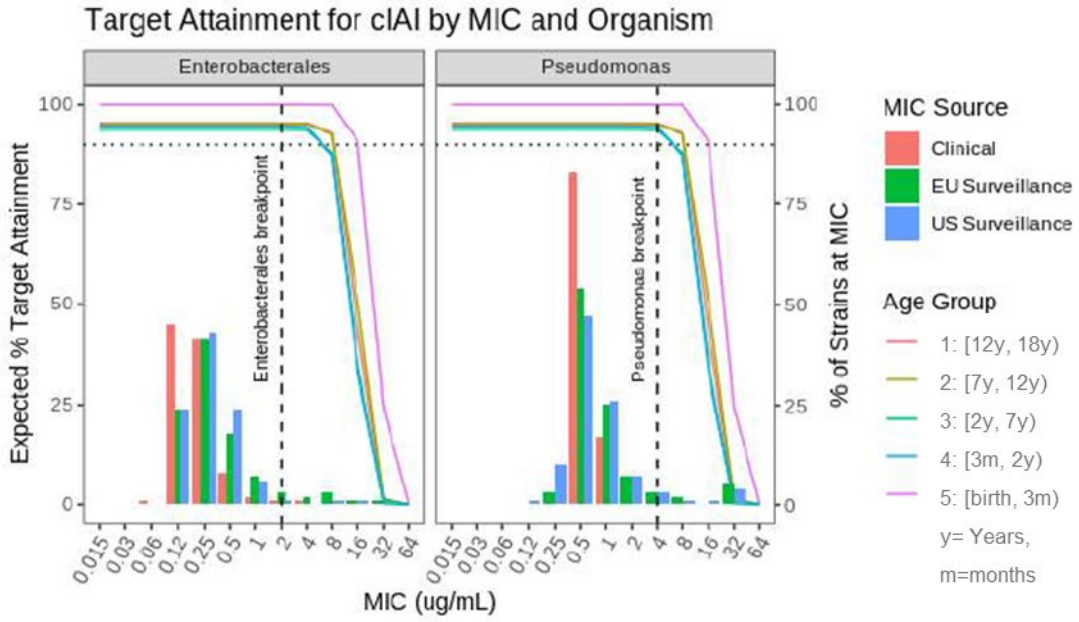
**Figure 18: Percentage of Pediatric cUTI Patients Achieving 30% fT>MIC for ceftolozane and 20% fT>CT in tazobactam in plasma at Steady State with Enterobacterales (Left Panel) *and P. aeruginosa* (Right Panel) MIC Distributions Amongst Isolates from P034 and Surveillance Data**




The dashed vertical line represents 2 µg/mL for enterobacterales (left panel) and MIC of 4 µg/mL for P. aeruginosa (right panel); the dashed horizontal line represents 90% PTA

Abbreviations: cIAI = Complicated intra-abdominal infection urinary tract infection; *f*T>MIC = A fraction of the dosing interval that plasma concentrations remain above the minimum inhibitory concentration, *f*T>CT = A fraction of the dosing interval that free plasma concentrations remain above a threshold concentration
*Source: Adapted from Applicant's 05qwch, Figure B on Page 21 (link).*

**Figure 19: Percentage of Pediatric cIAI Patients Achieving 30% fT>MIC for ceftolozane and 20% fT>CT in tazobactam in plasma at Steady State With Enterobacterales (Left Panel) and *P. aeruginosa* (Right Panel) MIC Distributions Amongst Isolates from P035 and Surveillance Data**




The dashed vertical line represents 2 µg/mL for enterobacterales (left panel) and MIC of 4 µg/mL for P. aeruginosa (right panel); the dashed horizontal line represents 90% PTA

Abbreviations: cIAI = Complicated intra-abdominal infection urinary tract infection; *f*T>MIC = A fraction of the dosing interval that plasma concentrations remain above the minimum inhibitory concentration, *f*T>CT = A fraction of the dosing interval that free plasma concentrations remain above a threshold concentration
*Source: Adapted from Applicant's 05qwch, Figure C on Page 21 (link).*

**Reviewer's analysis**

*The joint PTA curves were overlaid on a histogram illustrating the 2017 – 2019 surveillance data from the US and the EU, and the MIC distribution for P. aeruginosa and Enterobacterales isolates from P034 and P035. However, the simulated population showed higher exposures than those of population PK dataset, especially for pediatric group 5 with cUTI. Therefore, the PTA was evaluated based on the PPK data. In addition, the fT > MIC or CT is defined a fraction of the dosing interval that free plasma concentrations remain above a threshold concentration. However, in the Applicant's R codes, the protein bindings for ceftolozane (16% to 21%) and tazobactam (30%) were NOT involved. Based on the breakpoints of ceftolozane/tazobactam for Enterobacterales (MIC = 2 µg/mL) and P. aeruginosa (MIC =4 µg/mL), MIC value, 4 µg/mL, is selected for the PTA evaluation of ceftolozane. The PTA analysis results are shown in* Table 15-19. Percentage of Pediatric Patients Achieving 30% T>MIC (4 µg/mL) for Ceftolozane and 20% T>CT of 1 µg/mL for Tazobactam at the Proposed Dose Across all Age Groups by Total Plasma Concentration with MIC ***Table 15-19*** *based on ceftolozane/tazobactam plasma concentrations, and* ***Table 15-20*** *based on free ceftolozane/tazobactam concentrations. The*

*review team has found the fraction of pediatric patients achieving the target to be acceptable to support the proposed dosing regimen.*

**Table 15-19: Percentage of Pediatric Patients Achieving 30% T>MIC (4 µg/mL) for Ceftolozane and 20% T>CT of 1 µg/mL for Tazobactam at the Proposed Dose Across all Age Groups by Total Plasma Concentration with MIC**

| Study | AGECAT | Subject number | Joint PTA | Ceftolozane PTA | Tazobactam PTA |
|---|---|---|---|---|---|
| 34 | 1 | (b) (6) | 100 | 100 | 100 |
| 34 | 2 | | 100 | 100 | 100 |
| 34 | 3 | | 100 | 100 | 100 |
| 34 | 4 | | 100 | 100 | 100 |
| 34 | 5 | | 100 | 100 | 100 |
| 35 | 1 | | 100 | 100 | 100 |
| 35 | 2 | | 100 | 100 | 100 |
| 35 | 3 | | 100 | 100 | 100 |

**Table 15-20: Percentage of Pediatric patients Achieving 30% fT>MIC (4 µg/mL) for Ceftolozane and 20% fT>CT of 1 µg/mL for Tazobactam at the Proposed Dose Across all Age Groups by free Ceftolozane or Tazobactam concentration**

| Study | AGECAT | Subject number | Joint PTA | Ceftolozane PTA | Tazobactam PTA |
|---|---|---|---|---|---|
| 34 | 1 | (b) (6) | 100 | 100 | 100 |
| 34 | 2 | | 86.7 | 100 | 86.7 |
| 34 | 3 | | 100 | 100 | 100 |
| 34 | 4 | | 95.5 | 100 | 95.5 |
| 34 | 5 | | 100 | 100 | 100 |
| 35 | 1 | | 100 | 100 | 100 |
| 35 | 2 | | 100 | 100 | 100 |
| 35 | 3 | | 100 | 100 | 100 |

**1.7 Pediatric dose recommendation**

The Applicants' PTA, exposure and safety assessments based on the PPK model and simulation support the following dosing scheme in pediatric cUTI and cIAI pediatrics (birth to less 18 years of age with eGFR >50 mL/min/1.73 $m^2$).

- cIAI pediatrics, 30 mg/kg ( (b) (4)) up to a maximum dose of 1.5 g (b) (4)) every 8 hours with 5-14 days treatment.

- cUTI and pyelonephritis pediatrics, 30 mg/kg (b) (4) up to a maximum dose of 1.5 g (b) (4)) every 8 hours with 7-14 days treatment.

**Reviewer's comments:** *Based on the Reviewer's independent evaluation of pediatric exposure, PTA and safety based on PPK model, PPK dataset and estimates, the Reviewer agrees with the Applicants' pediatric dosage.*

## 15.3. Clinical Microbiology Review

The purpose of this efficacy supplement is to seek approval of Zerbaxa (ceftolozane/tazobactam) for treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in pediatric patients from birth to 18 years of age. Evidence to support the use of Zerbaxa in this age group is from clinical trials in adults with the same indications and PK and safety data from pediatric trials. From a clinical microbiology perspective, ceftolozane-tazobactam has previously shown activity against the indicated pathogens for cUTI and cIAI, including ESBL-producing isolates, in vitro and in animal studies. Some of the data previously submitted by the Applicant included in vitro data in pediatric populations from the US and Europe. All isolates in the SMART surveillance study, were greater than 93% susceptible to ceftolozane/tazobactam. Among US isolates of Enterobacterales, MIC90 was 0.5 mcg/mL. Among US isolates of *P. aeruginosa*, MIC90 was 2 mcg/mL. No new *in vitro* or *in vivo* studies were performed by the Applicant in support of the pediatric efficacy supplement. However, the Applicant did conduct microbiology evaluations in phase 2 clinical studies P034 and P035 as a secondary endpoint.

**Activity in vitro**
The Applicant provided MIC frequency distributions (histograms) that compared the susceptibility testing results of isolates from pediatric patients from 2017-2019 Surveillance Studies (SMART) of ceftolozane/tazobactam in vitro activity against *P. aeruginosa* and Enterobacterales and baseline isolates from the mMITT population in clinical studies P034 and P035 (not shown).

**Reviewer's Comment:** *The data from the MIC frequency distributions were similar between the surveillance and clinical trial isolates. No new information was provided on ceftolozane/tazobactam's mechanisms of action, mechanisms of resistance, or activity in vivo (animal studies).*

**Clinical Microbiology Analysis of Efficacy**

The microbiological endpoints were secondary endpoints, that were assessed in the mMITT and/or ME populations as described by the Applicant: The mMITT populations in P034 (95 participants) and P035 (82 (b) (4) were subsets of the randomized population which include participants that received study treatment and had at least 1 acceptable bacterial pathogen isolated from the baseline culture.

Baseline infecting pathogens were isolated from a quantitative culture (cUTI) or nonquantitative culture (cIAI) and were tested for susceptibility to ceftolozane/tazobactam and meropenem. For baseline pathogens the MIC cut-off values for susceptibility to Ceftolozane/tazobactam were ≤2 μg/mL for Enterobacterales, or ≤4 μg/mL for *P. aeruginosa*. The MIC cut-off values for susceptibility to meropenem were ≤1 μg/mL for Enterobacterales, and ≤2 μg/mL for *P. aeruginosa*.

A single central laboratory was used for confirmatory identification and susceptibility testing using broth microdilution following CLSI methodology. If a discrepancy existed regarding organism identification at the species level between the site and the central microbiology laboratory, the central microbiology laboratory data were used. If the discrepancy was at the genus level, both organisms were included. If no central laboratory data existed, local data were used. For each distinct pathogen identified for a subject, if the organism was cultured on more than one occasion per visit or 2 strains of the same species were isolated, a representative isolate was selected for use following a hierarchical algorithm developed by the Applicant until a single isolate remains:

1. Select the isolate obtained closest to (and prior to) the start time of dosing of study drug
2. Select the baseline isolate(s) with the highest MIC for C/T testing
3. Select the baseline isolate(s) with the highest MIC for MERO testing

If more than one isolate remained at this step, the isolates were considered equivalent and a representative isolate was selected from among them based on the lowest central microbiology laboratory accession number.

**Microbiological Evaluations in Phase 2 Clinical trials P034 and P035**

**P034 (cUTI)**

A favorable microbiological response at the TOC was defined by the Applicant as eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $<10^4$ CFU/mL of baseline uropathogens from the urine culture).

The Applicant reported that monomicrobial infections (overall 97.9%) were more common than polymicrobial infections (2.1%). A total of 160 bacterial isolates were identified, and

susceptibility tested at (b) (4) the central laboratory. This study included isolates identification through matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Among 113 Enterobacterales isolates, 97% were susceptible and 3% were intermediate to ceftolozane/tazobactam. The intermediate isolates to ceftolozane/tazobactam were 1 *K. pneumoniae* and 2 *S. marcescens*. Meropenem susceptibility was 99%. One baseline *K. pneumoniae* isolate was resistant to meropenem. All 90 *E. coli* tested were susceptible to ceftolozane/tazobactam and meropenem by MIC.

The Applicant reported that *E. coli,* and *K. pneumoniae* pathogens were the most prevalent species of Enterobacterales, isolated from 74 (77.9%) and 7 (7.4%) participants, respectively. Among all 88 participants with Enterobacterales, 4 (3 in the ceftolozane/tazobactam arm) were ESBL-positive. All 4 of the ESBL-positive isolates were *E. coli*. All the ESBL producing isolates were in *E. coli* and were clinical cures. Three were in the ceftolozane/tazobactam arm and one was in the meropenem arm. *P. aeruginosa* was isolated from 7 (7.4%) participants; AmpC-overexpression was not detected in any participants with *P. aeruginosa*.

A subset of Enterobacterales and *P. aeruginosa* baseline isolates were selected for additional molecular characterization at JMI based on predefined criteria. For example, a subset of 15 Enterobacterales isolates that had elevated MICs against cephalosporins, carbapenems, or ceftolozane/tazobactam were screened for beta-lactamases. The details of this study were provided in final study report 17-MER-04/MK7625 A-34. A total of 20 gram-negative isolates were evaluated by the Applicant for the presence of resistance determinants against β-lactam agents using whole genome sequencing analysis, quantitative RT-PCR, and Western blot analysis. This collection of isolates included 15 Enterobacterales, and 5 *P. aeruginosa*. Among the 15 Enterobacterales isolates, 1 carried genes encoding carbapenemases and 11 carried ESBL genes; a majority of these carried *bla*CTX-M-15 either alone or with other genes. Other *bla*CTX-M types were noted in an additional 5 isolates.

The Applicant reported that no isolate had an MIC of >4 mcg/mL and only 3 isolates had an MIC at 4 mcg/mL. ESBL-encoding genes were observed in 2 of the 5 *P. aeruginosa* isolates. Ceftolozane/tazobactam showed in vitro activity in isolates with elevated expression of efflux pumps (3 isolates). Two isolates of *P. aeruginosa* were resistant to ceftolozane-tazobactam (MIC >64 mcg/mL) in the same patient at baseline and at TOC; however, the participant was not in the mMITT population because the local site microbiology laboratory identified the isolates as *Pseudomonas fluorescens*. A genetic investigation demonstrated that this resistance was due to the acquisition of *bla*VEB-16 and an elevated expression of MexXY.

**Reviewer's Comment:** *The Applicant states that ceftolozane/tazobactam has activity against P. aeruginosa with elevated AmpC, "regardless of PDC allele", however it was noted that there were only 2 isolates, and there are a much larger number of PDC alleles, that were not tested. It was also noted that the two resistant P. aeruginosa isolates were from the same patient. VEB beta-lactamase, a class A beta-lactamase that appears frequently in nonfermenters (P.*

*aeruginosa) and Enterobacteriaceae spp., was detected, and is increasing in prevalence. Overexpression of an efflux pump was also detected*.

Summary of per pathogen clinical response at test of cure visit by MIC of baseline pathogen for ceftolozane/tazobactam in the microbiological modified intent-to-treat population is shown in the Applicant's table below:

**Table 15-21: Summary of Per-Pathogen Clinical Response at Test of Cure (TOC) Visit by MIC of Baseline Pathogen for Ceftolozane/Tazobactam Microbiological Modified Intent-to-Treat Population**

| **Pathogen Category** Organism **Group** Pathogen | Ceftolozane/ Tazobactam MIC (ug/mL) | C/T (N=71) | | | | MERO (N=24) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C n (%) | F n (%) | T | N1 | C n (%) | F n (%) |
| Aerobic GRAM-NEGATIVE | 0.06 - 4 | 68 | 67 | 60 (89.6) | 7 (10.4) | 24 | 23 | 22 (95.7) | 1 (4.3) |
| | 0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.12 | 29 | 28 | 26 (92.9) | 2 (7.1) | 9 | 8 | 8 (100.0) | 0 (0.0) |
| | 0.25 | 24 | 24 | 21 (87.5) | 3 (12.5) | 11 | 11 | 10 (90.9) | 1 (9.1) |
| | 0.5 | 10 | 10 | 9 (90.0) | 1 (10.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| | 1 | 2 | 2 | 1 (50.0) | 1 (50.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 2 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 4 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| Enterobacterales | 0.06 - 4 | 63 | 62 | 57 (91.9) | 5 (8.1) | 22 | 21 | 20 (95.2) | 1 (4.8) |
| | 0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.12 | 29 | 28 | 26 (92.9) | 2 (7.1) | 9 | 8 | 8 (100.0) | 0 (0.0) |
| | 0.25 | 24 | 24 | 21 (87.5) | 3 (12.5) | 11 | 11 | 10 (90.9) | 1 (9.1) |
| | 0.5 | 7 | 7 | 7 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 1 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 2 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Citrobacter spp.* | 0.25 - 0.25 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.25 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Enterobacter cloacae complex* | 0.25 - 0.5 | 3 | 3 | 3 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.25 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Escherichia coli* | 0.06 - 2 | 49 | 49 | 45 (91.8) | 4 (8.2) | 20 | 20 | 19 (95.0) | 1 (5.0) |
| | 0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.12 | 26 | 26 | 23 (88.5) | 3 (11.5) | 9 | 9 | 9 (100.0) | 0 (0.0) |
| | 0.25 | 19 | 19 | 18 (94.7) | 1 (5.3) | 10 | 10 | 9 (90.0) | 1 (10.0) |
| | 0.5 | 3 | 3 | 3 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 2 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Klebsiella oxytoca* | 0.12 - 0.12 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.12 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Klebsiella pneumoniae* | 0.12 - 1 | 6 | 6 | 6 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 0.12 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.25 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.5 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 1 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Proteus mirabilis* | 0.25 - 0.5 | 2 | 2 | 1 (50.0) | 1 (50.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |

| Pathogen Category<br>Organism **Group**<br>Pathogen | Ceftolozane/<br>Tazobactam<br>MIC (ug/mL) | C/T (N=71) | | | | MERO (N=24) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C<br>n (%) | F<br>n (%) | T | N1 | C<br>n (%) | F<br>n (%) |
| | 0.25 | 1 | 1 | 0 (0.0) | 1 (100.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Serratia marcescens* | 4 - 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| Pseudomonas aeruginosa | 0.5 - 4 | 5 | 5 | 3 (60.0) | 2 (40.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| | 0.5 | 3 | 3 | 2 (66.7) | 1 (33.3) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| | 1 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |

C/T=ceftolozane/tazobactam, MERO=meropenem
Participants are counted in the worst (highest) MIC category within baseline pathogen category and organism group.
n=Number of participants in specific category. T=Number of isolates.
N1=Number of participants in specific population having baseline pathogen categories with the corresponding C/T MIC value.
Percentages are calculated as 100 x (n/N1).
C=Clinical Cure, F=Clinical Failure.

Source: [P034MK7625A: adam-adsl; admbrsp; adeff]

Source: This submission.

**Reviewer's Comment:** *When comparing the MITT per-pathogen clinical response at TOC and the per pathogen microbiological outcome at TOC by MIC of baseline pathogen for ceftolozane/tazobactam, there were no notable discrepancies between the clinical cure/failure and microbial eradication/persistence. The Applicant reported that P. aeruginosa had a 60% clinical success and a 40% clinical failure at the lowest MIC values (0.5-4 mcg/mL), however, there were few numbers of isolates evaluated at those MIC values. Although there were few isolates of other bacteria as well, the trend was supportive of clinical success for the indicated pathogens tested.*

**Emergence of Resistance During Treatment**

The emergence of resistance across the 2 treatment arms for the mMITT population in P034 and P035 was evaluated. The Applicant defined this as a pathogen identified as susceptible at baseline, but resistant after baseline. In P034 and P035, no participants in either treatment arm developed resistance during treatment.

**Assessment of Superinfecting Pathogens and New Infecting Pathogens**

**P034**

The incidence of new infections was 4.2% and 0% of participants, in the ceftolozane/tazobactam and meropenem treatment arms, respectively. No superinfections were documented in either treatment arm. *P. aeruginosa (*2 participants) and *K. pneumoniae (*1 participant*)* were isolated from participants with new infections in the ceftolozane/tazobactam treatment arm.

**P035**

The incidence of both superinfections and new infections were 1.6% in the C/T treatment arm and 0% in the MERO treatment arm, respectively. *P. aeruginosa* was isolated from a participant with superinfection, while *K. pneumoniae* was isolated from a participant with a new infection. Both the superinfections and new infections were in the ceftolozane/tazobactam treatment arm.

**Breakpoints for cUTI and cIAI**
The ceftolozane/tazobactam breakpoints used in P034 and P035 were the existing approved breakpoints for cUTI and cIAI in adults. Provisional breakpoints of S/I/R ≤4/8/≥16 ug/ml were used by the Applicant for both ceftolozane/tazobactam and meropenem for any pathogen without current CLSI breakpoints.

**Clinical Trial Quality Control for in vitro Testing During Clinical Studies**
During the Phase 2 P034 and P035 studies, aerobic and anaerobic pathogens were tested at a central laboratory, (b) (4) Each isolate was identified, and susceptibility testing was performed by broth microdilution according to CLSI M07 guidelines. QC testing was performed using ATCC organism(s) on each day that clinical isolates were tested against ceftolozane/tazobactam and other antibiotics. For MIC testing of all organisms, (b) (4) produced frozen-form 96-well panels. The testing medium was cation-adjusted Mueller-Hinton broth.

**cIAI**
This was a Phase 2, randomized, blinded, multi-center, active controlled trial evaluating the safety and efficacy of ceftolozane/tazobactam plus metronidazole versus meropenem plus placebo in pediatric participants from birth to <18 years of age with cIAI.

The identification, antimicrobial susceptibility testing and characterization of resistance mechanisms of bacterial isolates from cIAI clinical pediatric trial were described in final study report 17-MER-05/MK7625A-035. A total of 217 bacterial isolates were identified and susceptibility tested at (b) (4) The Applicant reported that *E. coli* was the most prevalent species of Enterobacterales, isolated from 60 (65.9%) participants. Among all 60 Enterobacterales, 9 (15%) were ESBL-positive. *P. aeruginosa* was isolated from 25 (27.5%) participants and was the second most prevalent pathogen. AmpC-overexpression was detected in 1 (4%) of the participants with *P. aeruginosa*. *Bacteroides fragilis* were in 17 (18.6%) participants, and all were susceptible to ceftolozane/tazobactam, but activity was limited against *B. thetaiotamicron* isolates (MIC values 32-greater than 64 mcg/mL). Tested streptococci isolates were susceptible to ceftolozane/tazobactam.

A subset of Enterobacterales and *P. aeruginosa* baseline isolates were selected for additional molecular characterization at (b) (4) based on pre-defined criteria. A total of 19 gram-negative isolates were evaluated for the presence of resistance determinants against β-lactam agents using whole genome sequencing analysis, quantitative RT-PCR, and Western blot analysis. This collection of isolates included 18 Enterobacterales, and 1 *P. aeruginosa*.

There were 18 Enterobacterales isolates that met the criteria for β-lactamase screening and molecular testing. The Applicant reported that of the *E. coli* isolates tested, 14 carried ESBL genes and these genes included *CTX-M-15* (8 isolates), *CTX-M-55* (5 isolates), and *CTX-M-14* (1 isolate). Three *K. pneumoniae* isolates harbored ESBLs. One of these isolates carried *bla*KPC-3 in addition to *bla*CTX-M-15 and exhibited a ceftolozane/tazobactam MIC value of >64 µg/mL. The other two *K. pneumoniae* isolates harbored *bla*CTX-M-15 or *bla*SHV-18. The gene encoding the cefepimase OXA-1 (i.e., OXA-30), was detected in 1 *E. coli* and 1 K. *pneumoniae* in combination with *bla*CTX-M-15. The isolate carrying *bla*KPC-3 in addition to *bla*CTX-M-15 was resistant to ceftolozane/tazobactam (MIC >64). The 1 *P. aeruginosa* and 1 *Proteus vulgaris* group isolates screened for β-lactamases did not have the resistance mechanisms investigated.

**Reviewer's Comment:** *Molecular detection methods found ESBLs among some of the isolates tested in the cIAI clinical trial. One beta-lactamase included OXA-1, a penicillinase that is described in the literature as being a major correlate of resistance to piperacillin/tazobactam and found in isolates with other factors that narrow aminoglycoside treatment options (Livermore, et al. Journal of Antimicrobial Chemotherapy, Volume 74, Feb. 2019)*

The microbiological outcome categories and emergent infection categories are defined by the Applicant in the tables below.

**Table 15-22: Microbiological Outcome Categories**

| Outcome [a] | Definition |
|---|---|
| Eradication [b] | Absence of the baseline pathogen(s) in a postbaseline specimen appropriately obtained from the original site of infection. |
| Presumed eradication [b] | Absence of material to culture in a participant who was assessed as having partial improvement, or clinical cure. |
| Persistence | Presence of the baseline pathogen(s) in an appropriately obtained postbaseline specimen from the site of infection or surgical wound.<br>NOTE: Cultures from indwelling drains were not considered appropriate. |
| Presumed persistence | Absence of material to culture in a participant who was assessed as a clinical failure. |
| Persistence acquiring resistance | Presence of baseline pathogen(s) in an appropriately obtained postbaseline specimen where the baseline pathogen(s) was susceptible to study treatment pretreatment and is resistant to study treatment post-treatment. |
| Indeterminate | • Baseline culture either not obtained or has no growth.<br>• Postbaseline culture was not obtained and clinical assessment was not possible.<br>• Any other circumstance that makes it impossible to define the microbiological response (eg, participant lost to follow-up). |

[a] The per-pathogen microbiological outcome was determined for each baseline infecting pathogen isolated by the Sponsor.

[b] Eradication or presumed eradication was considered favorable microbiological responses. In order for the participant to have a favorable overall microbiological response (ie, eradication or presumed eradication), it was required that each baseline pathogen have a favorable microbiological outcome.

Source: This submission.

**Table 15-23: Emergent Infection Categories**

| Outcome | Definition |
|---|---|
| Superinfection | Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriately obtained postbaseline specimen in a subject while on study treatment. |
| New infection | Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriately obtained postbaseline specimen in a subject after administration of the last dose of study treatment and through the TOC visit. |

Source: This submission.

The Summary of Clinical Response at TOC by MIC of baseline pathogen for ceftolozane/tazobactam mMITT population is shown in the tables below:

**Table 15-24: Summary of Clinical Response at Test of Cure (TOC) Visit by MIC of Baseline Pathogen for Ceftolozane/Tazobactam Microbiological Modified Intent-to-Treat Population**

| Pathogen Category<br>Organism **Group**<br>Pathogen | Ceftolozane/<br>Tazobactam<br>MIC (ug/mL) | C/T+MTZ (N=63) | | | | MERO (N=19) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C<br>n (%) | F<br>n (%) | T | N1 | C<br>n (%) | F<br>n (%) |
| Aerobic Gram-Negative | <=0.03 - 1 | 70 | 51 | 45 (88.2) | 6 (11.8) | 20 | 17 | 17 (100.0) | 0 (0.0) |
| | <=0.03 | 2 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.12 | 22 | 15 | 13 (86.7) | 2 (13.3) | 7 | 5 | 5 (100.0) | 0 (0.0) |
| | 0.25 | 20 | 13 | 12 (92.3) | 1 (7.7) | 5 | 4 | 4 (100.0) | 0 (0.0) |
| | 0.5 | 21 | 17 | 15 (88.2) | 2 (11.8) | 7 | 7 | 7 (100.0) | 0 (0.0) |
| | 1 | 5 | 5 | 4 (80.0) | 1 (20.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| Enterobacterales | 0.12 - 1 | 49 | 44 | 38 (86.4) | 6 (13.6) | 14 | 13 | 13 (100.0) | 0 (0.0) |
| | 0.12 | 22 | 21 | 18 (85.7) | 3 (14.3) | 7 | 6 | 6 (100.0) | 0 (0.0) |
| | 0.25 | 19 | 17 | 15 (88.2) | 2 (11.8) | 4 | 4 | 4 (100.0) | 0 (0.0) |
| | 0.5 | 5 | 3 | 3 (100.0) | 0 (0.0) | 3 | 3 | 3 (100.0) | 0 (0.0) |
| | 1 | 3 | 3 | 2 (66.7) | 1 (33.3) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Escherichia coli* | 0.12 - 1 | 44 | 44 | 38 (86.4) | 6 (13.6) | 13 | 13 | 13 (100.0) | 0 (0.0) |
| | 0.12 | 21 | 21 | 18 (85.7) | 3 (14.3) | 7 | 7 | 7 (100.0) | 0 (0.0) |
| | 0.25 | 18 | 18 | 15 (83.3) | 3 (16.7) | 4 | 4 | 4 (100.0) | 0 (0.0) |
| | 0.5 | 4 | 4 | 4 (100.0) | 0 (0.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| | 1 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Klebsiella oxytoca* | 0.5 - 0.5 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 0.5 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |

| **Pathogen Category**<br>Organism **Group**<br>Pathogen | Ceftolozane/<br>Tazobactam<br>MIC (ug/mL) | C/T+MTZ (N=63)<br>T | N1 | C<br>n (%) | F<br>n (%) | MERO (N=19)<br>T | N1 | C<br>n (%) | F<br>n (%) |
|---|---|---|---|---|---|---|---|---|---|
| *Klebsiella pneumoniae* | 0.12 - 1 | 4 | 4 | 3 (75.0) | 1 (25.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.12 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.25 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 1 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Proteus vulgaris* | 1 - 1 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 1 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Comamonas* | <=0.03 - <=0.03 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | <=0.03 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Pseudomonas* | 0.5 - 0.5 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| Pseudomonas Aeruginosa | 0.25 - 1 | 18 | 18 | 16 (88.9) | 2 (11.1) | 6 | 6 | 6 (100.0) | 0 (0.0) |
| | 0.25 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 0.5 | 15 | 15 | 13 (86.7) | 2 (13.3) | 4 | 4 | 4 (100.0) | 0 (0.0) |
| | 1 | 2 | 2 | 2 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| Aerobic Gram-Positive | 0.12 - >64 | 14 | 13 | 10 (76.9) | 3 (23.1) | 10 | 9 | 9 (100.0) | 0 (0.0) |

| **Pathogen Category**<br>Organism **Group**<br>Pathogen | Ceftolozane/<br>Tazobactam<br>MIC (ug/mL) | C/T+MTZ (N=63)<br>T | N1 | C<br>n (%) | F<br>n (%) | MERO (N=19)<br>T | N1 | C<br>n (%) | F<br>n (%) |
|---|---|---|---|---|---|---|---|---|---|
| | 0.12 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.5 | 2 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 1 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 2 | 5 | 5 | 4 (80.0) | 1 (20.0) | 3 | 3 | 3 (100.0) | 0 (0.0) |
| | 4 | 4 | 4 | 3 (75.0) | 1 (25.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 32 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 64 | 2 | 2 | 1 (50.0) | 1 (50.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Enterococcus avium* | 64 - 64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Enterococcus durans* | >64 - >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Enterococcus faecalis* | 64 - 64 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 64 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Enterococcus faecium* | 32 - 64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 32 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |

| **Pathogen Category** Organism **Group** Pathogen | Ceftolozane/ Tazobactam MIC (ug/mL) | C/T+MTZ (N=63) | | | | MERO (N=19) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C n (%) | F n (%) | T | N1 | C n (%) | F n (%) |
| *Streptococcus anginosus* | 0.5 - 4 | 8 | 8 | 6 (75.0) | 2 (25.0) | 3 | 3 | 3 (100.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 2 | 4 | 4 | 3 (75.0) | 1 (25.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| | 4 | 3 | 3 | 2 (66.7) | 1 (33.3) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Streptococcus constellatus* | 2 - 4 | 2 | 2 | 2 (100.0) | 0 (0.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| | 2 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Streptococcus intermedius* | 0.5 - 1 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 1 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Streptococcus pneumoniae* | 0.12 - 0.12 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 0.12 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| Anaerobic Gram-Negative | <=0.06 - >64 | 27 | 14 | 12 (85.7) | 2 (14.3) | 7 | 5 | 5 (100.0) | 0 (0.0) |
| | <=0.06 | 3 | 0 | 0 (0.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 1 | 4 | 4 | 3 (75.0) | 1 (25.0) | 3 | 2 | 2 (100.0) | 0 (0.0) |
| | 2 | 8 | 3 | 3 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |

| **Pathogen Category** Organism **Group** Pathogen | Ceftolozane/ Tazobactam MIC (ug/mL) | C/T+MTZ (N=63) | | | | MERO (N=19) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C n (%) | F n (%) | T | N1 | C n (%) | F n (%) |
| | 4 | 2 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 16 | 1 | 0 | 0 (0.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 32 | 3 | 1 | 1 (100.0) | 0 (0.0) | 2 | 1 | 1 (100.0) | 0 (0.0) |
| | 64 | 3 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | >64 | 2 | 2 | 2 (100.0) | 0 (0.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| *Alistipes* | <=0.06 - <=0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | <=0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Bacteroides caccae* | 4 - 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Bacteroides dorei* | 32 - 32 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 32 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Bacteroides fragilis* | 0.5 - 4 | 12 | 12 | 10 (83.3) | 2 (16.7) | 3 | 3 | 3 (100.0) | 0 (0.0) |
| | 0.5 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 1 | 4 | 4 | 3 (75.0) | 1 (25.0) | 3 | 3 | 3 (100.0) | 0 (0.0) |
| | 2 | 6 | 6 | 6 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 4 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |

| **Pathogen Category** Organism **Group** Pathogen | Ceftolozane/ Tazobactam MIC (ug/mL) | C/T+MTZ (N=63) | | | | MERO (N=19) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C n (%) | F n (%) | T | N1 | C n (%) | F n (%) |
| *Bacteroides nordii* | 2 - 2 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 2 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Bacteroides thetaiotaomicron* | 32 - >64 | 4 | 4 | 4 (100.0) | 0 (0.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| | 32 | 2 | 2 | 2 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 64 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | >64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Bacteroides uniformis* | 32 - 64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 32 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Bacteroides vulgatus* | 16 - 16 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 16 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Bilophila wadsworthia* | >64 - >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Fusobacterium mortiferum* | >64 - >64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | >64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |

| **Pathogen Category** Organism **Group** Pathogen | Ceftolozane/ Tazobactam MIC (ug/mL) | C/T+MTZ (N=63) | | | | MERO (N=19) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C n (%) | F n (%) | T | N1 | C n (%) | F n (%) |
| *Fusobacterium nucleatum* | 2 - 2 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 2 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Parabacteroides distasonis* | >64 - >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Prevotella buccae* | <=0.06 - <=0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | <=0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Prevotella nigrescens* | <=0.06 - <=0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | <=0.06 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| Anaerobic Gram-Positive | <=0.06 - >64 | 7 | 6 | 4 (66.7) | 2 (33.3) | 3 | 2 | 2 (100.0) | 0 (0.0) |
| | <=0.06 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.25 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 4 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 8 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 16 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 0 | 0 (0.0) | 0 (0.0) |
| | >64 | 2 | 1 | 1 (100.0) | 0 (0.0) | 2 | 2 | 2 (100.0) | 0 (0.0) |
| *Bifidobacterium longum* | 16 - >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |

| Pathogen Category<br>Organism **Group**<br>Pathogen | Ceftolozane/<br>Tazobactam<br>MIC (ug/mL) | C/T+MTZ (N=63) | | | | MERO (N=19) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C<br>n (%) | F<br>n (%) | T | N1 | C<br>n (%) | F<br>n (%) |
| | 16 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Clostridium innocuum* | >64 - >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Clostridium perfringens* | <=0.06 - 0.25 | 3 | 3 | 2 (66.7) | 1 (33.3) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | <=0.06 | 2 | 2 | 2 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 0.25 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Clostridium ramosum* | 4 - 4 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | 4 | 1 | 1 | 0 (0.0) | 1 (100.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| *Clostridium tertium* | 8 - >64 | 1 | 1 | 1 (100.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| | 8 | 1 | 1 | 1 (100.0) | 0 (0.0) | 0 | 0 | 0 (0.0) | 0 (0.0) |
| | >64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |
| *Eggerthella lenta* | >64 - >64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |

| Pathogen Category<br>Organism **Group**<br>Pathogen | Ceftolozane/<br>Tazobactam<br>MIC (ug/mL) | C/T+MTZ (N=63) | | | | MERO (N=19) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | T | N1 | C<br>n (%) | F<br>n (%) | T | N1 | C<br>n (%) | F<br>n (%) |
| | >64 | 0 | 0 | 0 (0.0) | 0 (0.0) | 1 | 1 | 1 (100.0) | 0 (0.0) |

C/T=ceftolozane/tazobactam, MERO=meropenem, MTZ=metronidazole
Participants are counted in the worst (highest) MIC category within baseline pathogen category and organism group.
n=Number of participants in specific category. T=Number of isolates.
N1=Number of participants in specific population having baseline pathogen categories with the corresponding C/T MIC value.
Percentages are calculated as 100 x (n/N1).
C=Clinical Cure, F=Clinical Failure.

Source: [P035MK7625A: adam-adsl; admbrsp]

Source: This submission.

**Reviewer's Comment:** *It is noted that there were a limited number of isolates in the study and that some of the isolates listed are not isolates that are included in approved labeling such as the gram-negative aerobic organism from the genus Comamonas and a relatively new genus of bacteria, Alistipes, which sometimes includes isolates of the human gut microbiome.*

The Applicant's summary of superinfections and/or new infections in the mMITT population are shown in the table below:

**Table 15-25: Summary of Superinfection and/or New Infection Microbiological Modified Intent-to-Treat (mMITT) Population (P034)**

| | C/T | | | MERO | | |
|---|---|---|---|---|---|---|
| | n | (%) | 95% CI[a] | n | (%) | 95% CI[a] |
| Number of Participants | 71 | | | 24 | | |
| Participants with at least 1 Superinfection | 0 | (0.0) | | 0 | (0.0) | |
| Participants with at least 1 New Infection | 3 | (4.2) | (1.45, 11.70) | 0 | (0.0) | |
| *Klebsiella pneumoniae* | 1 | (1.4) | | 0 | (0.0) | |
| *Pseudomonas aeruginosa* | 2 | (2.8) | | 0 | (0.0) | |

C/T=ceftolozane/tazobactam, MERO=MEROpenem
[a] The 95% CIs of each treatment are unstratified Wilson CIs.
Every participant is counted a single time for each applicable row and column.
Superinfection: A urine culture grows ≥10^5 CFU/mL of an appropriate gram-negative uropathogena other than the baseline uropathogen(s) during the course of study treatment.
New Infection: A urine culture grows ≥10^5 CFU/mL of an appropriate gram-negative uropathogena other than the baseline uropathogen(s) after administration of the last dose of study treatment.

Source: [P034MK7625A: adam-adsl; admb]

Source: This submission.

**Table 15-26: Summary of Superinfection and/or New Infection Microbiological Modified Intent-to-Treat (mMITT) Population (P035)**

| | C/T+MTZ | | | MERO | | |
|---|---|---|---|---|---|---|
| | n | (%) | 95% CI[a] | n | (%) | 95% CI[a] |
| Number of Participants | 63 | | | 19 | | |
| Participants with at least 1 Superinfection | 1 | (1.6) | (0.28, 8.46) | 0 | (0.0) | |
| *Pseudomonas aeruginosa* | 1 | (1.6) | | 0 | (0.0) | |
| Participants with at least 1 New Infection | 1 | (1.6) | (0.28, 8.46) | 0 | (0.0) | |
| *Klebsiella pneumoniae* | 1 | (1.6) | | 0 | (0.0) | |

C/T=ceftolozane/tazobactam, MERO=MEROpenem, MTZ=Metronidazole
[a] The 95% CIs of each treatment are unstratified Wilson CIs.
Every participant is counted a single time for each applicable row and column.
Superinfection: Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriately obtained post-baseline specimen in a participant while on study treatment.
New Infection: Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriate obtained post-baseline specimen in a subject after completion of study treatment.

Source: [P035MK7625A: adam-adsl; admb]

Source: This submission.

**Final Clinical Microbiology Recommendations**

From a clinical microbiology perspective, the information provided by the Applicant supports the efficacy of ceftolozane/tazobactam for the treatment of susceptible bacteria for the indications of cUTI and cIAI in pediatric patients. Although not powered for efficacy determination, the reviewer notes that the clinical trial isolates from pediatric patients had MIC frequency distributions reflective of susceptibility to ceftolozane/tazobactam and high clinical and microbiological response rates in clinical trials in pediatric patients. No updates to Microbiology labeling or breakpoints are recommended at this time.

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**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.**

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/s/

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JACQUELYN C ROSENBERGER
04/20/2022 12:42:49 PM
Signing as proxy for Deborah Kim

KERIAN K GRANDE ROCHE
04/20/2022 12:46:50 PM

AVERY C GOODWIN
04/20/2022 12:55:00 PM

ANTHONY M NICASIO
04/20/2022 12:56:27 PM

ABHAY JOSHI
04/20/2022 01:11:39 PM

HEZHEN WANG
04/20/2022 01:13:31 PM

JUSTIN C EARP
04/20/2022 03:08:19 PM

KELLIE S REYNOLDS
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CHRISTOPHER E KADOORIE
04/20/2022 03:12:30 PM

DANIEL B RUBIN
04/20/2022 03:15:11 PM

JAE H HONG
04/20/2022 03:17:17 PM

MUKILAN NATARAJAN
04/20/2022 03:18:53 PM

HIWOT HIRUY
04/20/2022 03:22:57 PM

HIWOT HIRUY
04/20/2022 03:22:57 PM

GREGORY F DIBERNARDO
04/20/2022 03:25:27 PM

MAUREEN P DILLON PARKER
04/20/2022 04:00:47 PM

ABIMBOLA O ADEBOWALE
04/20/2022 04:06:48 PM

DMITRI IARIKOV
04/20/2022 04:10:03 PM

PETER W KIM
04/20/2022 04:13:38 PM