NDA Multi-Displinary Review and Evaluation

Application Type	Efficacy supplement
Application Number	NDA 212819/S008
Priority or Standard	Standard
Submit Date	February 13, 2025
Received Date	February 13, 2025
PDUFA Goal Date	December 13, 2025
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	See electronic signature date
Established/Proper Name	Imipenem, cilastatin, and relebactam
Trade Name	RECARBRIO
Pharmacologic Class	Combination of imipenem, a carbapenem antibacterial drug, cilastatin, a renal dehydropeptidase inhibitor, and relebactam a beta-lactamase inhibitor
Applicant	Merck Sharp & Dohme LLC
Dosage form	Powder for Injection, 1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) in a single-dose vial
Applicant Proposed Indications/Population	Addition of pediatric patients (aged birth to less than 18 years old) to the approved adult indications: • Complicated urinary tract infections, including pyelonephritis in patients who have limited or no alternative treatment options • Complicated intra-abdominal infections in patients who have limited or no alternative treatment options • Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia
Recommendation on Regulatory Action	Approval
Recommended Indications/Population	Treatment of the following infections caused by susceptible gram-negative microorganisms in adult and pediatric patients weighing at least 2 kg: • Complicated urinary tract infections including pyelonephritis in patients who have limited or no alternative treatment options • Complicated intra-abdominal infections in patients who have limited or no alternative treatment options • Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia
Recommended Dosing Regimen	Refer to Section 1 of this review

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Lori Kolejian
Chief, Regulatory Project Management Staff	Trang Tran
Nonclinical Reviewer	James Wild
Nonclinical Team Leader	Amy Nostrandt
Clinical Pharmacology Reviewer	Cristina Miglis
Clinical Pharmacology Team Leader	Dakshina Chilukuri
Pharmacometrics Reviewer	Xiaolei Pan
Pharmacometrics Team Leader	Justin Earp
Clinical Microbiology Reviewer	Kerian Grande Roche
Clinical Microbiology Team Leader	Avery Goodwin
Statistical Reviewer	Rafael Morsomme
Secondary Statistical Reviewer	Daniel Rubin
Product Quality Reviewer	George Lunn
Product Quality Team Leader	Dorota Matecka
Clinical Reviewer	Sanjay Revankar
Clinical and Cross-Disciplinary Team Leader	Mark Needles
Associate Director for Labeling	Abimbola Adebowale
Deputy Division Director (designated signatory authority)	Dmitri Iarikov

Additional Reviewers of Application

OPDP	Qumerunnisa Syed, Regulatory Review Officer Sam Skariah, Team Leader
OSE/DMEPA	Deborah Myers, Safety Evaluator Valerie Vaughan, Team Leader
OSE/DRM	Naomi Boston, Team Leader
DPMH	Shamir Tuchman, Senior Physician Mona Khurana, Team Leader

OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatrics and Maternal Health
DRM = Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Regulatory Project Manager	Lori Kolejian, MS, MAMB	Office of Regulatory Operations, Division of Regulatory Operations for Infectious Diseases, Anti-Infectives	Sections: 3	**Select one:** _x_ Authored ___ Approved
	Signature: LORI D. KOLEJIAN -S Digitally signed by LORI D. KOLEJIAN -S Date: 2025.12.08 12:34:27 -05'00'			
Chief Regulatory Project Management Staff	CAPT Trang Tran, PharmD, MBA, BCPS	Office of Regulatory Operations, Division of Regulatory Operations for Infectious Diseases, Anti-Infectives	Sections: 3	**Select one:** ___ Authored _x_ Approved
	Signature: TRANG Q. TRAN -S Digitally signed by TRANG Q. TRAN -S Date: 2025.12.08 12:40:38 -05'00'			
Nonclinical Reviewer	James Wild, PhD	Office of Infectious Diseases, Division of Pharmacology/Toxicology for Infectious Diseases	Sections: 4.2; 5.1	**Select one:** _x_ Authored ___ Approved
	Signature: James Wild -S Digitally signed by James Wild -S Date: 2025.12.08 12:51:37 -05'00'			
Nonclinical Supervisor	Amy Nostrandt, PhD	Office of Infectious Diseases, Division of Pharmacology/Toxicology for Infectious Diseases	Sections: 4.2; 5.1	**Select one:** ___ Authored _x_ Approved
	Signature: AMY C. NOSTRANDT -S Digitally signed by AMY C. NOSTRANDT -S Date: 2025.12.08 13:18:54 -05'00'			
Clinical Pharmacology Reviewer	Cristina Miglis, PharmD, MSc	Office of Clinical Pharmacology, Division of Infectious Disease Pharmacology	Sections: 6; 15.3	**Select one:** _x_ Authored ___ Approved
	Signature: CRISTINA M. MIGLIS -S Digitally signed by CRISTINA M. MIGLIS -S Date: 2025.12.08 12:26:10 -06'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Dakshina Chilukuri, PhD	Office of Clinical Pharmacology, Division of Infectious Disease Pharmacology	Sections: 6; 15.3	**Select one:** ___ Authored __x__ Approved
	Signature: Dakshina M. Chilukuri -S Digitally signed by Dakshina M. Chilukuri -S Date: 2025.12.08 13:29:23 -05'00'			
Pharmacometrics Reviewer	Xiaolei Pan, PhD	Office of Clinical Pharmacology, Division of Pharmacometrics	Sections: 15	**Select one:** __x__ Authored ___ Approved
	Xiaolei Pan -S Digitally signed by Xiaolei Pan -S Date: 2025.12.08 13:55:04 -05'00'			
Pharmacometrics Team Leader	Justin Earp, PhD	Office of Clinical Pharmacology, Division of Pharmacometrics	Sections: 15	**Select one:** ___ Authored __x__ Approved
	JUSTIN C. EARP -S Digitally signed by JUSTIN C. EARP -S Date: 2025.12.08 15:13:32 -05'00'			
Clinical Microbiology Reviewer	Kerian Grande Roche, PhD	Office of Infectious Diseases, Division of Anti-Infectives	Sections: 4.3	**Select one:** __x__ Authored ___ Approved
	Signature: AVERY C. GOODWIN -S Digitally signed by AVERY C. GOODWIN -S Date: 2025.12.09 09:56:16 -05'00'			
Clinical Microbiology Team Leader	Avery Goodwin, PhD	Office of Infectious Diseases, Division of Anti-Infectives	Sections: 4.3	**Select one:** ___ Authored __x__ Approved
	Signature: AVERY C. GOODWIN -S Digitally signed by AVERY C. GOODWIN -S Date: 2025.12.08 15:31:45 -05'00'			
Statistical Reviewer	Rafael Morsomme, PhD	Office of Biostatistics, Division of Biometrics IV	Sections: 8.1; 8.3; 8.4	Select one: __x__ Authored ___ Approved

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
	Signature: RAPHAEL MORSOMME -S	Digitally signed by RAPHAEL MORSOMME -S Date: 2025.12.08 15:56:45 -05'00'		
Secondary Statistical Reviewer	Daniel Rubin, PhD	Office of Biostatistics, Division of Biometrics IV	Sections: 8.1; 8.3; 8.4	**Select one:** ___ Authored _x_ Approved
	Signature: SCOTT S. KOMO -S	Digitally signed by SCOTT S. KOMO -S Date: 2025.12.08 16:45:52 -05'00'		
Product Quality Reviewer	George Lunn, PhD	Office of Pharmaceutical Quality	Sections: 4.2	**Select one:** _x_ Authored ___ Approved
	Signature: Dorota M. Matecka -S	Digitally signed by Dorota M. Matecka -S Date: 2025.12.09 09:08:35 -05'00'		
Product Quality Team Leader	Dorota Matecka, PhD	Office of Pharmaceutical Quality	Sections: 4.2	**Select one:** ___ Authored _x_ Approved
	Signature: Dorota M. Matecka -S	Digitally signed by Dorota M. Matecka -S Date: 2025.12.09 09:10:06 -05'00'		
Clinical Reviewer	Sanjay Revankar, MD	Office of Infectious Disease, Division of Anti-Infectives	Sections: 1; 2; 7; 8.2; 8.4; 9-13; 15.1	**Select one:** _x_ Authored ___ Approved
	Signature: SANJAY G. REVANKAR -S	Digitally signed by SANJAY G. REVANKAR -S Date: 2025.12.09 09:22:28 -05'00'		
Clinical Team Leader/ Cross-Disciplinary Team Leader	Mark Needles, MD	Office of Infectious Diseases, Division of Anti-Infectives	Sections: 1-15.1	**Select one:** ___ Authored _x_ Approved
	Signature: Mark Needles -S	Digitally signed by Mark Needles -S Date: 2025.12.09 10:27:00 -05'00'		

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling	Abimbola Adebowale, MS, PhD	Office of Infectious Diseases, Division of Anti-Infectives	Sections: 11	Select one: ___ Authored _x_ Approved
	Signature: Abimbola O. Adebowale -S Digitally signed by Abimbola O. Adebowale -S Date: 2025.12.09 11:29:16 -05'00'			
Deputy Division Director (Clinical)	Dmitri Iarikov, MD, PhD	Office of Infectious Diseases, Division of Anti-Infectives	Sections: 1-15	**Select one:** ___ Authored _x_ Approved
	Signature: {see appended electronic signature page}			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report

PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Imipenem-cilastatin-relebactam (IMI-REL, RECARBRIO, NDA 212819) is a fixed combination antibacterial drug product composed of imipenem, a carbapenem; cilastatin, a renal dehydropeptidase inhibitor that limits the renal metabolism of imipenem, and relebactam, a beta-lactamase inhibitor. Imipenem-cilastatin (PRIMAXIN, NDA 050587) was approved in 1985 for intravenous use and indicated for the treatment of the following serious infections caused by designated susceptible bacteria: lower respiratory tract infections, urinary tract infections, intra-abdominal infections, gynecologic infections, bacterial septicemia, bone and joint infections, skin and skin structure infections, and endocarditis in adult and pediatric patients. Imipenem-cilastatin is not indicated in patients with meningitis because safety and efficacy have not been established. Imipenem-cilastatin is not recommended in pediatric patients with central nervous system (CNS) infections because of the risk of seizures, and it is not recommended in pediatric patients weighing less than 30 kg with impaired renal function, as no data are available. Relebactam is a beta-lactamase inhibitor with activity against Ambler class A and C beta-lactamases and does not have intrinsic antibacterial activity.

RECARBRIO was initially approved in 2019 for use in adults who have limited or no alternative options for the treatment of: (1) complicated urinary tract infections, including pyelonephritis (cUTI) and (2) complicated intra-abdominal infections (cIAI) caused by susceptible gram-negative bacteria. A subsequent efficacy supplement for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) in adults was approved in 2020. The current efficacy supplement provides for the expansion of the adult indications for treatment of cUTI, cIAI, and HABP/VABP to include patients (birth to <18 years of age) weighing at least 2 kg. The inclusion of pediatric patients is supported by 2 studies: P020, a single dose pharmacokinetic study involving 46 pediatric patients, and P021, a randomized, active-comparator study involving 113 pediatric patients.

The proposed dosage of RECARBRIO for all indications in pediatric patients weighing at least 2 kg varies by patient weight and age as displayed in the table below. RECARBRIO is not recommended in pediatric patients less than 37 weeks post-menstrual age (gestational age at birth plus post-natal age).

Table 1. Recommended Dosage of RECARBRIO In Pediatric Patients Weighing at Least 2 kg

Age Range	Body Weight	Dose	Dosing Frequency	Infusion Duration
Birth[a] to < 3 months	2 kg or greater	37.5 mg/kg [b]	Every 8 hours	60 minutes
3 months < 18 years	less than 30 kg	37.5 mg/kg [b]	Every 6 hours	60 minutes
3 months to < 18 years	30 kg or greater	1.25 grams [c]	Every 6 hours	30 minutes

[a] Pediatric patients from birth (includes pediatric patients at least 37 weeks post-menstrual age)
[b] Provides 15 mg/kg imipenem, 15 mg/kg cilastatin, and 7.5 mg/kg relebactam
[c] Provides 500 mg imipenem, 500 mg cilastatin, and 250 mg, relebactam

Pediatric patients weighing at least 30 kg who have an estimated glomerular filtration rate (eGFR) less than 90 mL/min/1.73m^2 require dosage reduction of RECARBRIO as displayed in the table below. There is insufficient information to recommend a dosage of RECARBRIO for pediatric patients weighing less than 30 kg with any degree of renal impairment.

Table 2. Recommended Dosage of RECARBRIO in Pediatric Patients Weighing at Least 30 kg with Renal Impairment

eGFR (mL/min/1.73 m^2)[a]	Dose	Dosing Frequency	Infusion Duration
60 - 89	1 gram[b]	Every 6 hours	30 minutes
30 - 59	0.75 grams[c]	Every 6 hours	30 minutes
15- 29 not receiving hemodialysis	0.5 grams[d]	Every 6 hours	30 minutes
< 30 receiving hemodialysis	0.5 grams[d]	Every 6 hours	30 minutes
< 15 not receiving hemodialysis	Not recommended		

[a] Calculated using a GFR estimating equation validated in pediatric patients weighing at least 30 kg.
[b] Provides 400 mg imipenem, 400 mg cilastatin, and 200 mg relebactam
[c] Provides 300 mg imipenem, 300 mg cilastatin, and 150 mg relebactam
[d] Provides 200 mg imipenem, 200 mg cilastatin, and 100 mg relebactam

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided adequate information to support the effectiveness of IMI-REL in pediatric patients from birth to < 18 years of age for the treatment of cUTI (in patients with limited or no alternative treatment options), cIAI (in patients with limited or no alternative treatment options), and HABP/VABP.The substantial evidence of effectiveness of IMI-REL in the pediatric population is extrapolated from the clinical experience of IMI-REL in the treatment of adults with cUTI, cIAI and HABP/VABP through exposure matching to the established adult exposure ranges. The effectiveness of IMI-REL in pediatric patients is also supported by data from pediatric clinical studies including a single dose, pharmacokinetic study and a phase 2/3 open-label, randomized, active-controlled study in pediatric participants from birth to <18 years of age with confirmed or suspected gram-negative bacterial infections.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

IMI-REL is a fixed combination of imipenem, a penem antibacterial, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a beta-lactamase inhibitor with activity against Ambler class A and C beta-lactamases. IMI-REL is approved for the treatment of cUTI and cIAI caused by susceptible gram-negative microorganisms in adult patients who have limited or no treatment options, and for the treatment of HABP/VABP caused by susceptible gram-negative microorganisms in adult patients. In this supplemental NDA submission, the Applicant is seeking to expand the cUTI, cIAI, and HABP/VABP indications to include pediatric patients (birth to less than 18 years of age) weighing at least 2 kg.

Evaluation of the safety and efficacy of IMI-REL in the pediatric population relies on FDA's previous findings of safety and efficacy of IMI-REL in adults for the treatment of cUTI including pyelonephritis, cIAI and HABP/VABP. Clinical and pharmacokinetic data in pediatric patients were provided by studies P020, a single dose, pharmacokinetic study in 5 age groups, and P021, a phase 2/3 open-label, randomized, active-controlled study in pediatric participants from birth to <18 years of age with confirmed or suspected gram-negative bacterial infections. The majority of patients treated with IMI-REL or active control in Study P021 had cUTI or cIAI. Although there was no formal hypothesis testing for efficacy conducted due to small sample sizes, the clinical response at end of treatment was comparable between IMI-REL and active control arms in Study P021.

No new specific safety concerns related to IMI-REL were identified in the pediatric clinical trials. In the IMI-REL clinical program, 131 pediatric participants were exposed to any dose of IMI-REL and 85 pediatric participants received the proposed dose of IMI-REL. While the safety database is limited in pediatric patients, it is considered adequate for the proposed indications, particularly given the known safety profile of IMI-REL in adult patients.

Overall, the Applicant has provided adequate information to support use of IMI-REL for the treatment of cUTI and cIAI in pediatric patients weighing at least 2 kg who have limited or no alternative treatment options, and for the treatment of HABP/VABP in pediatric patients weighing at least 2 kg.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the pediatric population, complicated urinary tract infections (cUTI) may be defined as UTIs with associated conditions such as abnormalities of the urinary tract and systemic symptoms, often requiring hospitalization. Pyelonephritis is a subset of cUTI regardless of other factors. Most cUTIs are caused by Enterobacterales, though	• cUTI, cIAI and HABP/VABP are serious, potentially life-threatening infections causing significant morbidity and mortality in pediatric patients. • Increasing antimicrobial resistance, particularly among gram-negative pathogens is a public health concern and cUTI, cIAI and HABP/VABP caused by

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Staphylococcus saprophyticus and *Streptococcus agalactiae* may be common in specific age groups. • Complicated intra-abdominal infections (cIAI), which extend into the peritoneal space and may be associated with peritonitis or abscess formation are commonly seen with appendicitis in pediatric patients. Enterobacterales and anaerobic pathogens are typically involved in these infections. • Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia (HABP/VABP) in the pediatric population is associated with increased length of stay and higher morbidity and mortality, especially in intensive care unit (ICU) patients. Common bacteria include *Staphylococcus aureus* and Gram-negative bacteria such as *Pseudomonas aeruginosa*, and Gram-negative Enterobacteriaceae. • Resistant gram-negative pathogens, particularly carbapenem-resistant Enterobacterales (CRE) are of increasing concern due to lack of anti-bacterial agents available to adequately treat these infections.	CRE are of special concern due to limited treatment options.
Current Treatment Options	• Antibacterial drugs approved for the treatment of cUTI, cIAI or HABP/VABP in pediatric patients include extended-spectrum penicillins, cephalosporins, beta-lactam/beta-lactamase inhibitor combinations, fluoroquinolones, carbapenems, monobactams, aminoglycosides, tetracyclines and sulfonamides. • Recently approved antibacterial drugs for pediatric patients that may provide options for treatment of infections such as cUTI, cIAI and HABP/VABP caused by resistant gram-negative pathogens include ceftazidime-avibactam (2024) and ceftolozane-tazobactam (2022). • There remains, however, the need for additional options for treatment of infections, including for cUTI, cIAI and HABP/VABP caused by CRE.	There are several classes of antibacterial drugs approved for the treatment of serious infections in the pediatric population. Some recently approved antibacterial drugs may provide options for treatment of infections caused by resistant gram-negative pathogens. There remains, however, a need for additional options for the treatment of MDR infections, including in cUTI, cIAI and HABP/VABP, particularly caused by CRE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of IMI-REL in pediatric patients from birth to <18 years of age with suspected or confirmed gram-negative bacterial infections is extrapolated from the clinical experience of IMI-REL in the treatment of adults with cUTI, cIAI and HABP/VABP through exposure matching (AUC and Cmax) to the established adult exposure ranges. The safety and efficacy evaluation of IMI-REL is also supported by data from the pediatric clinical trials.	The efficacy and safety of IMI-REL in the treatment of cUTI, cIAI and HABP/VABP in pediatric patients is supported by the Agency's prior findings of efficacy of IMI-REL in these infections in adult patients, as well as PK and clinical data from the pediatric clinical trials.
Risk and Risk Management	• No new specific safety concerns were seen with IMI-REL in pediatric patients. No serious risks related to IMI-REL in children that would necessitate specific risk management strategies have been identified.	Labeling and routine pharmacovigilance will be adequate to communicate and monitor safety concerns with IMI-REL in the pediatric population at this time.

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

2 Therapeutic Context

2.1. Analysis of Condition

Infections such as cUTI including pyelonephritiscIAI and HABP/VABP caused by multi-drug resistant (MDR) gram-negative pathogens in pediatric patients are an increasing concern, both in the United States and globally. WHO has identified priority pathogens to include carbapenem-resistant *Acinetobacter baumannii* (CRAB), third-generation cephalosporin-resistant Enterobacterales, and carbapenem-resistant Enterobacterales (CRE)[1]. In Enterobacterales, the primary antibiotic resistance mechanism is the production of β-lactamases, including extended spectrum beta-lactamases (ESBL), AmpC and carbapenemases, hence the utility of novel beta-lactam/beta-lactamase inhibitor combinations in therapy.

Clinical risk factors for MDR bacterial colonization and infection for children include prematurity and low weight at birth, travel outside metropolitan area, immunosuppression, underlying chronic disease, previous hospitalization, intensive care unit stay, exposure to pediatric long-term care facilities, prior antibiotic use, and indwelling devices[2,3]. Up to 60% of hospitalized patients receive antibiotics, a known risk factor for resistance[4]. In the U.S., rates of ESBL and CRE in pediatric patients increased from 0.28% and 0% in 1999 to 0.92% and 0.47% in 2011, respectively[3]. Outcomes of MDR infections in pediatric patients depend upon the local epidemiology, timely identification of the pathogen and initiation of appropriate therapy, and the patient's clinical condition[4]. A study in 2013 estimated 15% of childhood deaths were due to sepsis, with MDR pathogens increasingly implicated, though limited data are available[3].

In the neonatal period, gram-negative bacteria are responsible for approximately 15-30% of late-onset infections (after 3 days), with *E. coli* and *Klebsiella* most often implicated[5]. In addition, maternal colonization with MDR pathogens may have a role in transmission to the infant, with potential for

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[1] Chiusaroli L et al. Tackling multidrug-resistant Gram-negative infections in children globally: current therapeutic options and perspectives. Expert Opin Pharmacother. 2025 Jul;26(10):1205-1220.
[2] Bassetti M et al. Optimal Management of Complicated Infections in the Pediatric Patient: The Role and Utility of Ceftazidime/Avibactam. Infect Drug Resist. 2020 Jun 12;13:1763-1773.
[3] Folgori L, Bielicki J. Future Challenges in Pediatric and Neonatal Sepsis: Emerging Pathogens and Antimicrobial Resistance. J Pediatr Intensive Care. 2019 Mar;8(1):17-24.
[4] Venuti F et al. Novel Beta Lactam Antibiotics for the Treatment of Multidrug-Resistant Gram-Negative Infections in Children: A Narrative Review. Microorganisms. 2023 Jul 13;11(7):1798.
[5] Flannery DD et al. Neonatal multidrug-resistant gram-negative infection: epidemiology, mechanisms of resistance, and management. Pediatr Res. 2022 Jan;91(2):380-391.

subsequent development of neonatal sepsis[6]. High rates of resistance in neonates to first and second line therapies (>40%) have been noted[3].

While MDR infections in pediatric patients overall remains low, rates in immuno-compromised patients are significantly higher, ranging from 3-17% in one study of pediatric liver transplant patients[7]. A large retrospective study of 1,291 bloodstream infections in pediatric patients with allogeneic HSCT or those receiving chemotherapy, more than 25% of gram-negative infections were MDR, with CRE representing 9% of infections[8]. These MDR infections were significantly associated with ICU admission and death. Prior exposure to antibiotics, especially third generation cephalosporins and carbapenems, has been significantly associated with MDR bloodstream infections and post-transplant infections in pediatric patients with hematologic malignancy, HSCT, and liver transplantation.

Many antibiotics active against MDR pathogens have not been well-studied in pediatric patients, resulting in limited pharmacokinetic data and uncertain dosing strategies[7]. As a result, there is a significant impact of these issues in pediatrics. Older antibiotics, such as fosfomycin, nitrofurantoin, aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole (TMP-SMX) have significant limitations related to antimicrobial spectrum and toxicities. Of note, use of polymyxin B in pediatric patients for MDR pathogens has increased in recent years, though limited data on PK/PD make optimal dosing challenging[9].

To counter these threats of MDR infections, there have been recent additions to the antimicrobial armamentarium, including ceftolozane/tazobactam (CT-TZ), ceftazidime/avibactam (CAZ-AVI), meropenem/vaborbactam (MER-VAB), imipenem/relebactam (IMI-REL), and cefiderocol. Currently, only ceftolozane/tazobactam (CT-TZ) and ceftazidime/avibactam (CAZ-AVI) are approved for pediatric use in the U.S. Additional anti-bacterial agents are needed to treat MDR pathogens in the pediatric population.

2.2. Analysis of Current Treatment Options

Table below lists currently available anti-bacterial agents approved for use in pediatric patients with gram-negative infections in the setting of cUTI, cIAI and HABP/VABP.

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[6] Bulabula ANH et al. Transmission of multidrug-resistant Gram-negative bacteria from colonized mothers to their infants: a systematic review and meta-analysis. J Hosp Infect. 2020 Jan;104(1):57-67.
[7] Dong SW et al. Approach to multidrug resistant infections in pediatric transplant recipients. Front Pediatr. 2023 Dec 7;11:1270564.
[8] Castagnola E et al. Antibiotic resistant bloodstream infections in pediatric patients receiving chemotherapy or hematopoietic stem cell transplant: factors associated with development of resistance, intensive care admission and mortality. Antibiot Basel Switz. (2021) 10(3):266.
[9] Karageorgos SA et al. Intravenous colistin use for infections due to MDR Gram-negative bacilli in critically ill paediatric patients: a systematic review and meta-analysis. J Antimicrob Chemother. 2019 Sep 1;74(9):2497-2506.

Table 3. Anti-bacterial agents approved for use in pediatric patients with cUTI, cIAI and HABP/VABP

Drug Name	Relevant Indication	Approved Age Range for Indication	Comments
Cephalosporins			
Cefuroxime sodium	UTI, Lower respiratory tract infections	≥ 3 months	Use as empiric monotherapy has declined with emergence of multi-drug resistant gram-negative bacilli
Ceftriaxone	cUTI, IAI, Lower respiratory tract infections	All ages	
Ceftazidime	cUTI, IAI, Lower respiratory tract infections	All ages	
Cefepime	cUTI, cIAI, Moderate to severe pneumonia	≥ 2 months	
Beta-Lactam/Beta-Lactamase Inhibitor Combinations			
Piperacillin-Tazobactam	IAI, Nosocomial pneumonia	≥ 2 months	
Ceftolozane-Tazobactam	cUTI, cIAI	All ages	
Ceftazidime-Avibactam	cUTI, cIAI, HABP/VABP	All ages	
Carbapenems			
Meropenem	cIAI	All ages	
Imipenem-Cilastatin	cUTI, cIAI, Lower respiratory tract infections	All ages	
Ertapenem	cUTI, cIAI, Community-acquired pneumonia	≥ 3 months	
Monobactams			
Aztreonam	cUTI, IAI, Lower respiratory tract infections	≥ 9 months	Although used in patients with allergy to penicillins/cephalosporins, there are concerns about cross-reactivity with ceftazidime
Aminoglycosides			
Gentamicin sulfate	Serious Infections	All ages	Risk of nephrotoxicity and ototoxicity
Tobramycin sulfate	cUTI, IAI, Lower respiratory tract infections	All ages	

Amikacin sulfate	Serious Infections	All ages	
Fluoroquinolones			
Ciprofloxacin	cUTI	≥ 1 year	Risk of tendonitis, tendon rupture, QTc prolongation, exacerbation of myasthenia gravis, CNS effects, peripheral neuropathy
Other classes			
Colistin	Serious Infections	All ages	Risk of nephrotoxicity
Trimethoprim-Sulfamethoxazole	UTI	≥ 2 months	

Source: Clinical reviewer

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant, Merck Sharp & Dohme LLC (Merck), submitted an investigational new drug (IND) application for imipenem/cilastatin/relebactam on September 13, 2010 (IND 108754). On September 13, 2013, the Division of Anti-Infectives granted the qualified infectious disease product and fast track designations for the treatment of complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/ VABP).

On November 16, 2018, Merck submitted the original New Drug Application (NDA) 212819 for Recarbrio (imipenem/cilastatin/relebactam powder for injection) which received approval on July 16, 2019, for the treatment of cUTI and cIAI in adult patients who have limited or no alternative therapeutic options. These adult indications for Recarbrio were then expanded to include the treatment of HABP/VABP through an efficacy supplement (NDA 212819/S-002) submitted on December 4, 2019, reviewed as a priority review sNDA due to QIDP designation for these indications, and subsequently approved on June 4, 2020.

This new efficacy supplement (NDA 212819/S-008), submitted on February 13, 2025, seeks to expand currently approved adult indications for Recarbrio to include pediatric patients (birth to less than 18 years old). This supplement was filed on April 22, 2025 has been granted as a standard review status, with a PDUFA goal date of December 13, 2025.

This submission also seeks to fulfill the following outstanding Pediatric Research Equity Act (PREA) postmarketing requirement listed in the June 4, 2020, approval letter for NDA 212819/S-002:

3865-1: Conduct a randomized, open-label, active controlled trial to evaluate the safety and tolerability of imipenem, cilastatin and relebactam in children from birth to less than 18 years of age with complicated urinary tract infections, complicated intra-abdominal infections and hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia.

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

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections have been conducted during the review of this supplemental NDA.

4.2. Product Quality

This supplement does not contain any updates to the Chemistry, Manufacturing and Controls section or Nonclinical section of the original NDA submission. The formulation proposed for use in pediatric patients is the same as the currently marketed product approved for adults.

4.3. Clinical Microbiology

4.3.1. Executive Summary

The clinical microbiology in vitro data in this pediatric study supplement supports the extension of indication for IMI-REL to pediatric patients aged birth to <18 years. No changes to the breakpoints for IMI-REL are proposed or recommended by the Agency or the Applicant.

4.3.2. Mechanism of Action and In Vitro Activity

Recarbrio is a combination of imipenem, a penem antibacterial, cilastatin, a renal dyhydropeptidase inhibitor, and relebactam, a beta-lactamase inhibitor with activity against class A/C beta-lactamases, including PDC and KPC enzymes. No new mechanism of action studies were done in this submission, and the same mechanism that applies in adults also applies to pediatric patients.

4.3.3. Surveillance Data and IMI-REL Breakpoints

Data on the IMI-REL minimum inhibitory concentrations (MICs) against *P. aeruginosa*, *Acinetobacter calcoaceticus baumannii*, and Enterobacterales from SMART Surveillance Studies in 2020 to 2022 are shown in Table 4, Table 5, and Table 6, respectively.

Table 4. Summary Statistics of IMI-REL MICs (mcg/mL) From SMART Surveillance Studies in 2020-2022 Combined Among *Pseudomonas aeruginosa* Pediatric Isolates

Region	N	µg/mL		% Susceptible			
		MIC Range	MIC_{50}	MIC_{90}	Mode MIC	CLSI	EUCAST
Europe	431	≤0.12 - >16	0.5	2	0.5	91.2	91.2
United States	195	≤0.12 - 16	0.5	2	0.5	92.3	92.3
Global	1600	≤0.12 - >16	0.5	2	0.5	90.6	90.6

CLSI=Clinical Laboratory Standards Institute; EUCAST=European Committee on Antimicrobial Susceptibility Testing; MIC=minimum inhibitory concentration; MIC_{50}= minimum inhibitory concentration required to inhibit the growth of 50% of the isolates; MIC_{90}= minimum inhibitory concentration required to inhibit the growth of 90% of the isolates; N=number of participants; REL=relebactam; SMART=Study for Monitoring Antimicrobial Resistance Trends
Source: [Ref. 5.3.5.4: 08NF8R]

Table 5. Summary Statistics of IMI-REL MICs (mcg/mL) from SMART Surveillance Studies in 2020-2022 Combined Among *Acinetobacter calcoaceticus baumannii* complex Pediatric Isolates

Region	N	µg/mL				
		MIC Range	MIC_{50}	MIC_{90}	Mode MIC	% Susceptible FDA
Europe	40	≤0.12 - >16	>16	>16	>16	40.0
United States	15	0.12 - 16	0.25	>16	0.25	86.7
Global	281	≤0.12 - >16	>16	>16	>16	35.9

MIC=minimum inhibitory concentration; MIC_{50}= minimum inhibitory concentration required to inhibit the growth of 50% of the isolates; MIC_{90}= minimum inhibitory concentration required to inhibit the growth of 90% of the isolates; N=number of participants; REL=relebactam; SMART=Study for Monitoring Antimicrobial Resistance Trends
Source: [Ref. 5.3.5.4: 08NF8R]

Table 6. Summary Statistics of IMI-REL MICs (mcg/mL) from SMART Surveillance Studies in 2020 to 2022 Combined Among Enterobacterales Pediatric Isolates

Organism	Region	N	µg/mL				% Susceptible	
			MIC Range	MIC_{50}	MIC_{90}	Mode MIC	CLSI	EUCAST
Key Enterobacterales	Europe	1060	≤0.12 - >8	0.12	0.25	≤0.12	99.3	99.4
Citrobacter freundii	Europe	17	≤0.12 -0.5	0.12	0.25	≤0.12	100	100
Citrobacter koseri	Europe	9	≤0.12 – 0.25	0.12	0.25	≤0.12	100	100
Enterobacter cloacae	Europe	45	≤0.12 – 4	0.12	0.25	≤0.12	97.8	97.8
Escherichia coli	Europe	683	≤0.12 – 1	0.12	0.25	≤0.12	100	100
Klebsiella aerogenes	Europe	8	≤0.12 – 0.25	0.12	0.25	≤0.12	100	100
Klebsiella oxytoca	Europe	74	≤0.12 – 4	0.12	0.25	≤0.12	98.6	98.6
Klebsiella pneumoniae	Europe	189	≤0.12 – >8	0.12	0.5	≤0.12	97.4	97.9
Serratia marcescens	Europe	35	0.25 - 1	0.5	0.5	0.5	100	100
Key Enterobacterales	US	612	≤0.12 – 2	0.25	0.5	≤0.12	99.0	100
Citrobacter freundii	US	22	≤0.12 – 0.25	0.25	0.25	0.25	100	100
Citrobacter koseri	US	10	≤0.12 – 1	0.12	0.25	≤0.12	100	100
Enterobacter cloacae	US	31	≤0.12 – 0.5	0.25	0.5	0.25	100	100
Escherichia coli	US	306	≤0.12 – 1	0.12	0.25	≤0.12	100	100
Klebsiella aerogenes	US	19	≤0.12 – 1	0.25	0.5	0.25	100	100
Klebsiella oxytoca	US	56	≤0.12 – 0.5	0.25	0.5	0.25	100	100
Klebsiella pneumoniae	US	103	≤0.12 – 1	0.25	0.5	0.25	100	100
Serratia marcescens	US	65	0.25 - 2	0.5	1	0.5	90.8	100
Key Enterobacterales	Global	4834	≤0.12 – >8	0.12	0.5	≤0.12	96.9	97.6
Citrobacter freundii	Global	70	≤0.12 – 0.5	0.25	0.25	0.25	100	100
Citrobacter koseri	Global	54	≤0.12 – 0.5	0.12	0.25	≤0.12	100	100
Enterobacter cloacae	Global	167	≤0.12 – 8	0.25	0.5	0.25	98.8	98.8
Escherichia coli	Global	2815	≤0.12 – >8	0.12	0.25	≤0.12	98.9	99.0
Klebsiella aerogenes	Global	81	0.25 - 2	0.25	0.5	0.25	98.8	100
Klebsiella oxytoca	Global	239	≤0.12 – >8	0.25	0.5	0.25	99.2	99.2
Klebsiella pneumoniae	Global	1174	≤0.12 – >8	0.25	1	≤0.12	91.7	92.8
Serratia marcescens	Global	234	≤0.12 – >8	0.5	1	0.5	92.3	99.1

CLSI=Clinical Laboratory Standards Institute; MIC=minimum inhibitory concentration; MIC_{50}= minimum inhibitory concentration required to inhibit the growth of 50% of the isolates; MIC_{90}= minimum inhibitory concentration required to inhibit the growth of 90% of the isolates; N=number of participants; REL= relebactam; SMART=Study for Monitoring Antimicrobial Resistance Trends

Source: [Ref. 5.3.5.4: 08NF8R]

- *Pseudomonas aeruginosa*: IMI/REL susceptibility exceeded 90% in all regions for combined isolates from all infection types using the MIC susceptible breakpoint of ≤ 2 mcg/mL.
- *Acinetobacter calcoaceticus-baumannii* complex: Susceptibility was >85% for US isolates but ≤40% for EU and global sources using a susceptible breakpoint of ≤ 2 mcg/mL.
- Enterobacterales: Most species showed susceptibility rates between 95-100% using the MIC susceptible breakpoint of ≤ 1 mcg/mL.

Reviewer's Comment

The percent of *P. aeruginosa* and Enterobacterales isolates susceptible to IMI-REL from pediatric patients was overall comparable for global, European, and the United States isolates.

For *A. calcoaceticus-baumannii* complex, the percent of susceptible isolates was significantly lower for global and European isolates than isolates of the United States.

The frequency of isolation of the top 20 gram-negative pathogens from adults and pediatric patients is shown in the tables of US SMART surveillance below.

Table 7. Frequency of Isolates of Top 20 Gram-negative Pathogens from Adult Patients from United States (US) SMART Surveillance Data (2020-2022)

Region	Age	Source	Year Collected	Organism	n	%
All Pathogens, N					10846	
US	Adult	All	2020-2022	*Escherichia coli*	3284	30.3
US	Adult	All	2020-2022	*Pseudomonas aeruginosa*	2082	19.2
US	Adult	All	2020-2022	*Klebsiella pneumoniae*	1575	14.5
US	Adult	All	2020-2022	*Proteus mirabilis*	504	4.6
US	Adult	All	2020-2022	*Klebsiella oxytoca*	408	3.8
US	Adult	All	2020-2022	*Klebsiella aerogenes*	404	3.7
US	Adult	All	2020-2022	*Serratia marcescens*	390	3.6
US	Adult	All	2020-2022	*Stenotrophomonas maltophilia*	344	3.2
US	Adult	All	2020-2022	*Enterobacter sp*	256	2.4
US	Adult	All	2020-2022	*Enterobacter cloacae*	241	2.2
US	Adult	All	2020-2022	*Klebsiella variicola*	210	1.9
US	Adult	All	2020-2022	*Citrobacter freundii*	208	1.9
US	Adult	All	2020-2022	*Citrobacter koseri*	192	1.8
US	Adult	All	2020-2022	*Acinetobacter baumannii*	190	1.8
US	Adult	All	2020-2022	*Morganella morganii*	152	1.4
US	Adult	All	2020-2022	*Enterobacter bugandensis*	104	1.0
US	Adult	All	2020-2022	*Providencia stuartii*	93	0.9
US	Adult	All	2020-2022	*Serratia sp*	82	0.8
US	Adult	All	2020-2022	*Enterobacter hormaechei*	69	0.6
US	Adult	All	2020-2022	*Raoultella ornithinolytica*	58	0.5

N = Total number of isolates for top 20 pathogens.
% = (n/N) x 100
A total of 11697 isolates were observed across 122 pathogens.

Source: [Ref. 5.3.5.4: 08NF8R]

Table 8. Frequency of Isolates of Top 20 Gram-Negative Pathogens from Pediatric Patients from United States (US) SMART Surveillance Data (2020 to 2022)

Region	Age	Source	Year Collected	Organism	n	%
All Pathogens, N					1139	
US	Peds	All	2020-2022	*Escherichia coli*	355	31.2
US	Peds	All	2020-2022	*Pseudomonas aeruginosa*	201	17.6
US	Peds	All	2020-2022	*Klebsiella pneumoniae*	117	10.3
US	Peds	All	2020-2022	*Serratia marcescens*	71	6.2
US	Peds	All	2020-2022	*Klebsiella oxytoca*	65	5.7
US	Peds	All	2020-2022	*Stenotrophomonas maltophilia*	65	5.7
US	Peds	All	2020-2022	*Proteus mirabilis*	47	4.1
US	Peds	All	2020-2022	*Enterobacter sp*	39	3.4
US	Peds	All	2020-2022	*Enterobacter cloacae*	29	2.5
US	Peds	All	2020-2022	*Citrobacter freundii*	24	2.1
US	Peds	All	2020-2022	*Klebsiella aerogenes*	21	1.8
US	Peds	All	2020-2022	*Morganella morganii*	15	1.3
US	Peds	All	2020-2022	*Acinetobacter baumannii*	14	1.2
US	Peds	All	2020-2022	*Serratia sp*	13	1.1
US	Peds	All	2020-2022	*Acinetobacter sp*	12	1.1
US	Peds	All	2020-2022	*Citrobacter koseri*	12	1.1
US	Peds	All	2020-2022	*Enterobacter hormaechei*	12	1.1
US	Peds	All	2020-2022	*Acinetobacter nosocomialis*	10	0.9
US	Peds	All	2020-2022	*Enterobacter bugandensis*	9	0.8
US	Peds	All	2020-2022	*Acinetobacter pittii*	8	0.7

N = Total number of isolates for top 20 pathogens.
% = (n/N) x 100
A total of 1243 isolates were observed across 69 pathogens.

Source: [Ref. 5.3.5.4: 08NF8R]

Surveillance data demonstrate that the 3 most frequently isolated gram-negative pathogens in pediatric and adult patients in the U.S. are *E. coli, P. aeruginosa,* and *K. pneumoniae*.

Reviewer's Comment
The information provided by the Applicant and reported in the literature on the frequency of clinical isolates and in vitro activity of IMI-REL against indicated organism indicate that the current IMI-REL breakpoints are relevant for pediatric patients. Currently FDA recognizes the Clinical and Laboratory Standards Institute (CLSI) IMI-REL MIC and zone diameter breakpoints for Enterobacterales, *P. aeruginosa*, and anaerobes; MIC breakpoints are presented below.

	Minimum Inhibitory Concentrations (mcg/mL)		
	Susceptible	Intermediate	Resistant
Enterobacterales*	≤1/4	2/4	≥4/4
P. aeruginosa	≤2/4	4/4	≥8/4
Anaerobes	≤4/4	8/4	≥16/4

*Breakpoints do not apply to the family *Morganellaceae.*

In addition, FDA identified IMI-REL MIC breakpoints (mcg/mL) for *Acinetobacter calcoaceticus-baumannii* complex and *Haemophilus influenzae* as presented below.

	Minimum Inhibitory Concentrations (mcg/mL)		
	Susceptible	Intermediate	Resistant
Acinetobacter calcoaceticus-baumannii complex	≤2/4	4/4	≥8/4
Haemophilus influenzae	≤4/4	-	-

4.3.4. Microbiological Methodology and Assessments in Study P021

Microbiological Response Assessment
Microbiological response was evaluated on a by-pathogen basis, with investigators determining response ratings based on local laboratory results relative to baseline pathogens. The sponsor categorized overall microbiological response as "favorable" or "unfavorable" based on the response of all baseline pathogens. Participants less than 3 months of age required meningitis exclusion prior to enrollment, as imipenem is not indicated for CNS infections due to seizure risk. The study allowed flexible active control selection based on local standard of care, acknowledging variation in clinical practice across healthcare facilities. Overall, no formal efficacy conclusions could be made from P021, as the study was not powered for formal hypothesis testing. There was a limited number of bacterial isolates (<10) except for *E. coli* and *P. aeruginosa*.

Specimen Collection Requirements
• HABP/VABP: Baseline lower respiratory tract specimens obtained within 48 hours of screening for Gram stain, culture, and susceptibility testing. Post-baseline specimens collected only when clinically indicated from participants requiring procedures allowing specimen collection. Expectorated or induced sputum samples also accepted if not met criteria to prevent contamination.

• cIAI: Baseline intra-abdominal specimens from purulent material collected within 24-48 hours of study intervention initiation. Post-baseline specimens obtained only during clinically indicated reinterventions.
• cUTI: Baseline urine specimens collected within 48 hours prior to study intervention, with specific colony count requirements (≥10^5 CFU/mL for midstream clean-catch or indwelling catheter specimens, ≥10^4 CFU/mL if blood culture positive, or ≥10^2 CFU/mL for straight catheter specimens). Post-baseline specimens collected at multiple timepoints throughout the study.

Central Laboratory Analysis
A single central laboratory conducted confirmatory identification and susceptibility testing using validated broth microdilution following CLSI methodology. All organisms considered pathogens by investigators were submitted for central laboratory analysis.

The by pathogen microbiological response definitions at various time points are shown in the tables below.

Table 9. By-Pathogen Microbiological Response Definitions at the EOIV and EOT Visits

Microbiological Response[a,b,c]	Response Definition
Eradication	HABP/VABP: A lower respiratory tract culture taken at the EOT visit[c] shows eradication of the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EOIV or EOT visit[c] shows eradication of the pathogen found at study entry. cUTI: A urine culture taken at the EOIV or EOT visit[c] shows eradication of the uropathogen (eg, ≥10^5 CFU/mL is reduced to <10^4 CFU/mL) found at study entry.
Presumed Eradication	No specimen taken because participant is deemed clinically improved or cured of the pathogen found at study entry.
Persistence[d]	HABP/VABP: A lower respiratory tract culture taken at the EOT visit[c] grows the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EOIV or EOT visit[c] grows the pathogen found at study entry. cUTI: A urine culture taken at the EOIV or EOT visit[c] shows the uropathogen (eg, ≥10^5 CFU/mL not reduced to <10^4 CFU/mL) found at study entry.
Superinfection	An infection-site culture grows a pathogen other than a baseline pathogen during the course of IV study intervention **OR** emergence during IV study intervention of a new pathogen at a distant sterile site along with worsening signs and symptoms of infection.
Indeterminate	a) Follow-up culture is not available at the EOIV or EOT visit[c] due to participant death or withdrawal from study; **OR** b) Available microbiological data are incomplete; **OR** c) Extenuating circumstances (eg, a major protocol violation) preclude microbiological assessment; **OR** d) Any other circumstance which makes it impossible to define the microbiological response.

Microbiological Response[a,b,c]	Response Definition
CFU = colony-forming unit; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; EOIV = end of IV therapy; EOT = end of therapy; HABP/VABP = hospital-acquired or ventilator-associated bacterial pneumonia; IV = intravenous a. A microbiological response rating must be completed separately for each pathogen isolated at study entry. If a new/emergent pathogen is identified at this visit which was not identified at baseline, the microbiological response rating should be recorded as "superinfection" for any new/emergent pathogen isolated after initiation of IV study therapy. b. A favorable by-pathogen microbiological response at EOT requires "eradication" or "presumed eradication" of the pathogen found at study entry. c. If a culture is not available at EOT, an assessment at this visit can be made from the last available culture collected after at least 72 hours of IV study intervention. If a culture is not available at EOT for cIAI or cUTI participants who receive oral switch, an assessment at this visit can be made from the last available culture collected after at least 48 hours of oral study intervention. d. If a participant is discontinued from IV or oral study intervention due to clinical failure (ie, unfavorable clinical response), but persistence of the admission pathogen is not confirmed by culture results or no culture is obtained at the time of clinical failure, the admission pathogen will be presumed to have persisted.	

Source: The Applicant's table in this submission

Table 10. By Pathogen Microbiological Response Definitions at the EFU and LFU Visits

Microbiological Response[a,b,c]	Response Definition
Eradication	HABP/VABP: A lower respiratory tract culture taken at the EFU or LFU[c] visit shows eradication of the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EFU or LFU visit[c] shows eradication of the pathogen found at study entry. cUTI: A urine culture taken at the EFU or LFU visit[c] shows eradication of the uropathogen (eg, $\geq 10^5$ CFU/mL is reduced to $<10^4$ CFU/mL) found at study entry.
Presumed Eradication	No specimen taken because participant is deemed clinically improved or cured of the pathogen found at study entry.
Persistence	An infection site culture taken at the EFU or LFU visit grows the pathogen found at study entry.
New Infection	A pathogen other than an original microorganism found at study entry is present in the infection site specimen any time after completion of IV or oral study intervention; **OR** A pathogen is isolated from a distant sterile site after completion of IV or oral study intervention.
Recurrence	An infection site culture grows the baseline pathogen taken any time after documented eradication.
Indeterminate	a) Follow-up culture is not available at the EFU or LFU visit due to participant death or withdrawal from study; **OR** b) Available microbiological data are incomplete; **OR** c) Extenuating circumstances (e.g., a major protocol violation) preclude microbiological assessment; **OR** d) Any other circumstance which makes it impossible to define the microbiological response.

Microbiological Response[a,b,c]	Response Definition
CFU = colony-forming unit; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; EFU = early follow-up; HABP/VABP = hospital-acquired or ventilator-associated bacterial pneumonia; IV = intravenous; LFU = late follow-up [a] A microbiological response rating must be completed separately for each pathogen isolated at study entry. If a new/emergent pathogen is identified at this visit which was not identified at study entry, the microbiological response rating should be recorded as "new infection" for any new/emergent pathogen isolated after initiation of IV study intervention. [b] A favorable by-pathogen microbiological response at the EFU or LFU visit requires "eradication" or "presumed eradication" of the pathogen found at study entry. [c] If a culture is not available at EFU or LFU, an assessment at this visit can be made based on the culture collected at EOT as long as it was collected at least 24 hours after the completion of IV or oral study intervention and before the EFU or LFU visit and provided the participant had fully resolved clinical symptoms/signs of the index infection at the EFU or LFU visit.	

Source: The Applicant's table in this submission

Baseline Pathogen Distribution

In the modified intent-to-treat (mMITT) population of 90 participants, baseline gram-negative aerobic bacilli were isolated in 84 (93.3%) participants. *E. coli* was the most prevalent species (63 participants, 70.0%), followed by *P. aeruginosa* (15 participants, 16.7%). The MIC90 of the baseline *E. coli* isolates in the IMI/REL group is:

- cUTI *E. coli* isolates (N=16): MIC_{90} = 0.5 mcg/mL
- cIAI *E. coli* isolates (N=32): MIC_{90} = 0.25 mcg/mL

Resistance

Molecular characterization of imipenem isolates:

• Enterobacterales: Among 4 evaluated isolates, 3/4 were susceptible to IMI-REL. Resistance mechanisms included NDM-1, KPC-2, AmpC beta-lactamases (CMY-1, DHA-1), and various extended-spectrum beta-lactamases (ESBLs).

• *P. aeruginosa*: Among 3 evaluated isolates, 1/3 were susceptible to IMI-REL. Resistance mechanisms included VEB-9 ESBL and chromosomally encoded AmpC-type enzymes (PDC-11, PDC-374).

The proportion of favorable clinical response at EOT for key baseline pathogens identified from infection site culture by baseline IMI-REL MIC (microbiological modified Intent-to treat population) is shown in the table below. Clinical response was ≥ 83% for all pathogens identified and at all MICs.

Table 11. Proportion of Favorable By-Pathogen Microbiological Response at EOT for Key Baseline Pathogens Identified from Infection Site Culture by Baseline Imipenem/REL MIC Microbiological Modified Intent-to-treat Population

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	Imipenem/REL MIC (µg/mL)	IMI/REL n/N (%)	Active Control n/N (%)
Participants in population*		56	19
Aerobic Gram-Negative Bacilli			
Enterobacter cloacae	0.25	0	0/1 (0.0)
Escherichia coli	0.06	3/3 (100.0)	0
	0.12	34/35 (97.1)	15/15 (100.0)
	0.25	6/6 (100.0)	0
	0.5	3/3 (100.0)	0
	1	1/1 (100.0)	0
Klebsiella aerogenes	0.12	1/1 (100.0)	0
Klebsiella oxytoca	0.12	2/2 (100.0)	0
	0.25	1/1 (100.0)	0
Klebsiella pneumoniae	0.12	2/2 (100.0)	0
	0.5	1/1 (100.0)	0
	16	0	1/1 (100.0)
Pseudomonas aeruginosa	0.5	9/10 (90.0)	2/3 (66.7)
	4	1/1 (100.0)	0
	8	1/1 (100.0)	0
Aerobic Gram-Negative Coccobacillus			
Haemophilus influenzae	≤ 0.03	0	1/1 (100.0)
	0.25	1/1 (100.0)	0

* Number of MMITT participants who have at least one key baseline pathogen from infection site culture with MIC data available.
N = number of pathogens with the specified MIC.
n = number of pathogens in the specific category.
% = (n/N) x 100.
MIC= minimum inhibitory concentration.
IMI/REL = imipenem/cilastatin/relebactam for treatment group and imipenem/relebactam for susceptibility testing;
The active control group includes the following IV drugs: cefepime, cefotaxime, ceftazidime, ceftriaxone, ceftriaxone and metronidazole, ciprofloxacin, ertapenem, imipenem, meropenem, piperacillin/tazobactam.

Source: [P02IMK7655A: adam-adsl; admbl; adms; adeff]

Source: The Applicant's table in this submission

Breakpoints

No changes to breakpoints for IMI-REL were proposed by the Applicant.

4.3.5. Clinical Microbiology Conclusions

The comprehensive microbiological data, including the surveillance MIC data provided by the Applicant, support the use of IMI-REL in pediatric patients with the targeted infection types. Refer to the clinical, statistical and clinical pharmacology reviews for additional information. No changes to the approved breakpoints are recommended for IMI-REL.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology or toxicology information was submitted with this supplement. A definitive subcutaneous and intravenous toxicity and toxicokinetic study with relebactam in juvenile rats was reviewed with the original NDA submission. The reader is referred to Dr. James Wild's review of the pharmacology/toxicology data submitted in the original NDA submission.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology information submitted in this supplemental NDA supports the approval of imipenem/cilastatin/relebactam for the treatment of complicated urinary tract infections, complicated intra-abdominal infections, and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia in pediatric patients birth to <18 years of age.

The clinical pharmacology profile of imipenem, cilastatin and relebactam in adults has been characterized and detailed in the original marketing application (NDA 212819). OCP's recommendations and comments on key review issues related to this supplement are summarized in theTable 12 table below.

Table 12. Summary of OCP Recommendations and Comments on Key Review Issues

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>Pivotal or supportive evidence of effectiveness</td><td>The pivotal efficacy evidence for IMI-REL in pediatric patients birth to <18 years of age with suspected or confirmed gram-negative bacterial infections is based on extrapolation from adult efficacy studies through exposure matching (AUC and Cmax) to the established exposure ranges in adult patients with cUTI, cIAI and HABP/VABP.

Imipenem and relebactam exposures assessed by population PK modeling showed AUC and Cmax in pediatric patients were comparable to adult exposures, with both falling within the established adult clinical experience range (5th to 95th percentiles) where safety and efficacy have been demonstrated.</td></tr>
<tr><td>General Dosing Instructions</td><td>Recommended Dosing Regimens for Imipenem/cilastatin/relabactam in Pediatric Patients Birth to Less than 18 years of Age

<table><tr><td>Body Weight</td><td>Age</td><td>Dose (imipenem/cilastatin and relebactam)</td><td>Dosing Frequency</td><td>Infusion Duration</td></tr></table></td></tr>
</table>

	2 kg to < 30 kg	≥3 months to < 18 years	37.5 mg/kg (imipenem 15 mg/kg, cilastatin 15 mg/kg and relebactam 7.5 mg/kg)	Every 6 hours	60 minutes
		Birth to <3 months	37.5 mg/kg (imipenem 15 mg/kg, cilastatin 15 mg/kg and relebactam 7.5 mg/kg)	Every 8 hours	60 minutes
	≥30 kg	<18 years	1.25 g (imipenem 500 mg, cilastatin 500 mg,relebactam 250 mg)	Every 6 hours	30 minutes
Dosing in patient subgroups (intrinsic and extrinsic factors)	A 30 kg weight threshold is the primary intrinsic factor to be considered when selecting the appropriate dosing regimen. Dose reduction is required in pediatric patients ≥30 kg with any degree of renal impairment (mild through ESRD). Population PK modeling supported these renal impairment dose adjustments for pediatric patients ≥30 kg and <18 years old, resulting in AUC and Cmax values that are similar to adults with normal renal function. RECARBRIO is not recommended in pediatric patients weighing <30 kg with renal impairment as no supporting data are available.				
Labeling	The Applicant's proposed labeling required minor modifications. Specific content and formatting recommendations have been provided to the Applicant by the review team.				

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides evidence of effectiveness through efficacy extrapolation based on exposure matching. This approach is appropriate given the similar disease pathophysiology, causative pathogens, and treatment response between adults and children for gram-negative bacterial infections.

The PK of imipenem and relebactam were evaluated in two pediatric studies: one phase 1b single-dose pharmacokinetic study (P020) and one phase 2/3 multiple-dose study (P021) in pediatric patients from birth to <18 years of age with confirmed or suspected gram-negative bacterial infections. Population PK analysis included 517 concentrations each for imipenem and relebactam from 131 pediatric participants, with final models incorporating fixed allometric body weight scaling, renal maturation function effects, and estimated glomerular filtration rate covariate relationships.

Model-based simulations demonstrated that the proposed pediatric dosing regimens achieve imipenem and relebactam exposures comparable to adults, with pediatric steady-state exposures (AUC and Cmax)

falling within those associated with the approved doses in adults for both cIAI/cUTI and HABP/VABP indications. Additionally, the Applicant conducted probability of target attainment (PTA) analyses demonstrating >90% of virtual pediatric patients would achieve both imipenem (40% fT>MIC) and relebactam (fAUC0-24h/MIC ≥8) pharmacokinetic/pharmacodynamic targets at the MIC of 2 µg/mL using the recommended dosing regimens.

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

The proposed weight-based dosing regimen is appropriate for the general pediatric population (birth to <18 years). Population pharmacokinetic modeling demonstrates both the fixed dosage for patients ≥30 kg and weight-based dosing for patients <30 kg achieve imipenem and relebactam exposures comparable to adults, supporting efficacy extrapolation while maintaining the established safety profile.

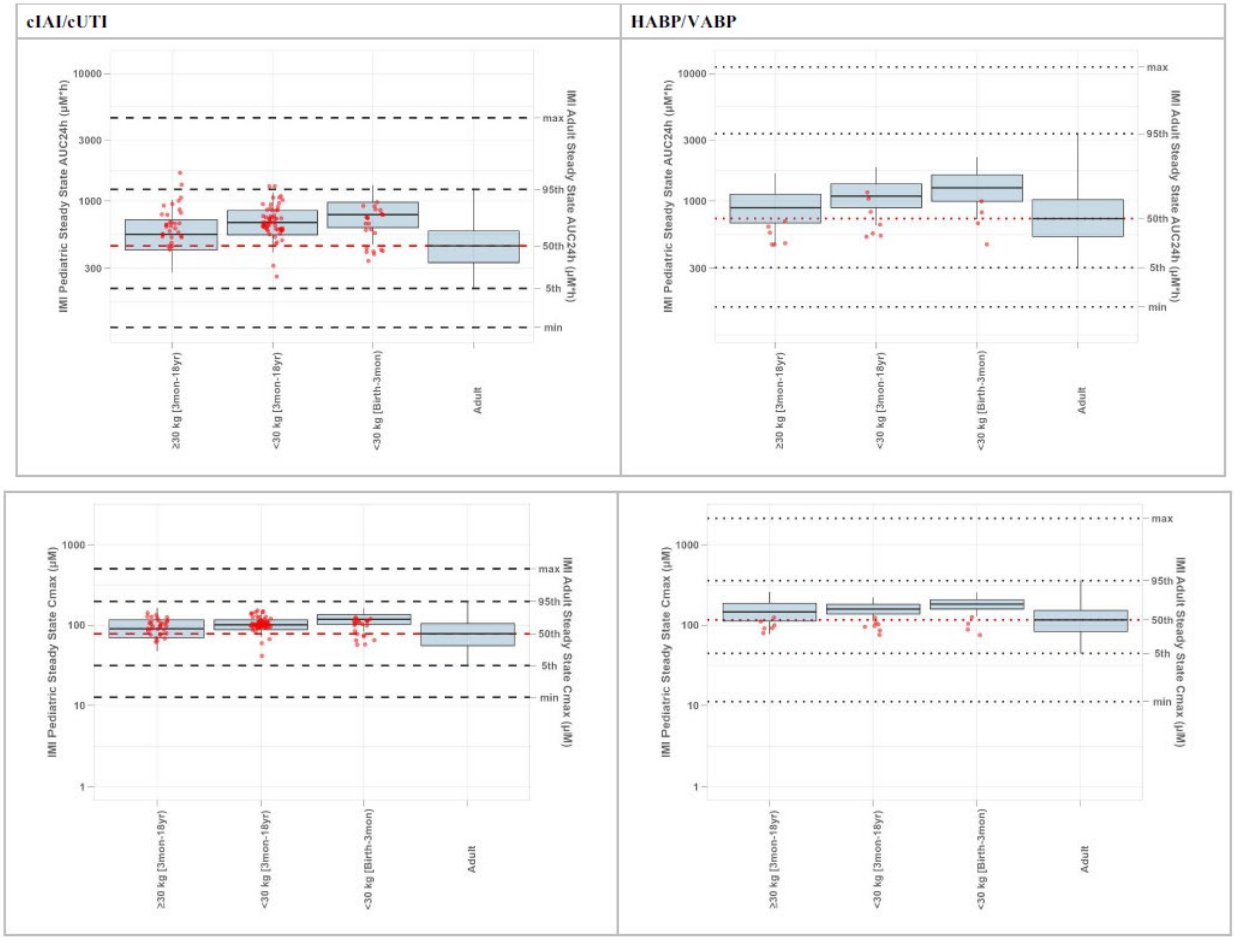
Fixed Dosage for Pediatric Patients ≥30 kg with Normal Renal Function
The fixed dosage recommendation for pediatric patients ≥30 kg is based on pharmacokinetic similarity to adults, evidence of comparable drug exposures, and practical clinical advantages.

Population PK modeling demonstrated that pediatric patients weighing ≥30 kg have clearance and volume of distribution characteristics sufficiently similar to adults when accounting for body size. In studies P020 and P021, all participants ≥12 to <18 years weighed >43 kg and received the adult dose, and approximately 32% of participants 6 to <12 years of age received the adult dose based on the 30 kg cutoff with an acceptable safety profile. These clinical study participants are representative of the general pediatric population based on an analysis using NHANES data demonstrating the 30 kg weight cutoff is achieved by 10 to 12 years of age in the general population.

The fixed dosage in patients weighing ≥30 kg with normal renal function achieved comparable imipenem and relebactam AUC and Cmax to adults with normal renal function (see Figure 1 and Figure 2). Additionally, this dosing strategy offers practical advantages by allowing pediatric patients ≥30 kg to receive the same 30-minute infusion duration as adults, while patients <30 kg require a 60-minute infusion.

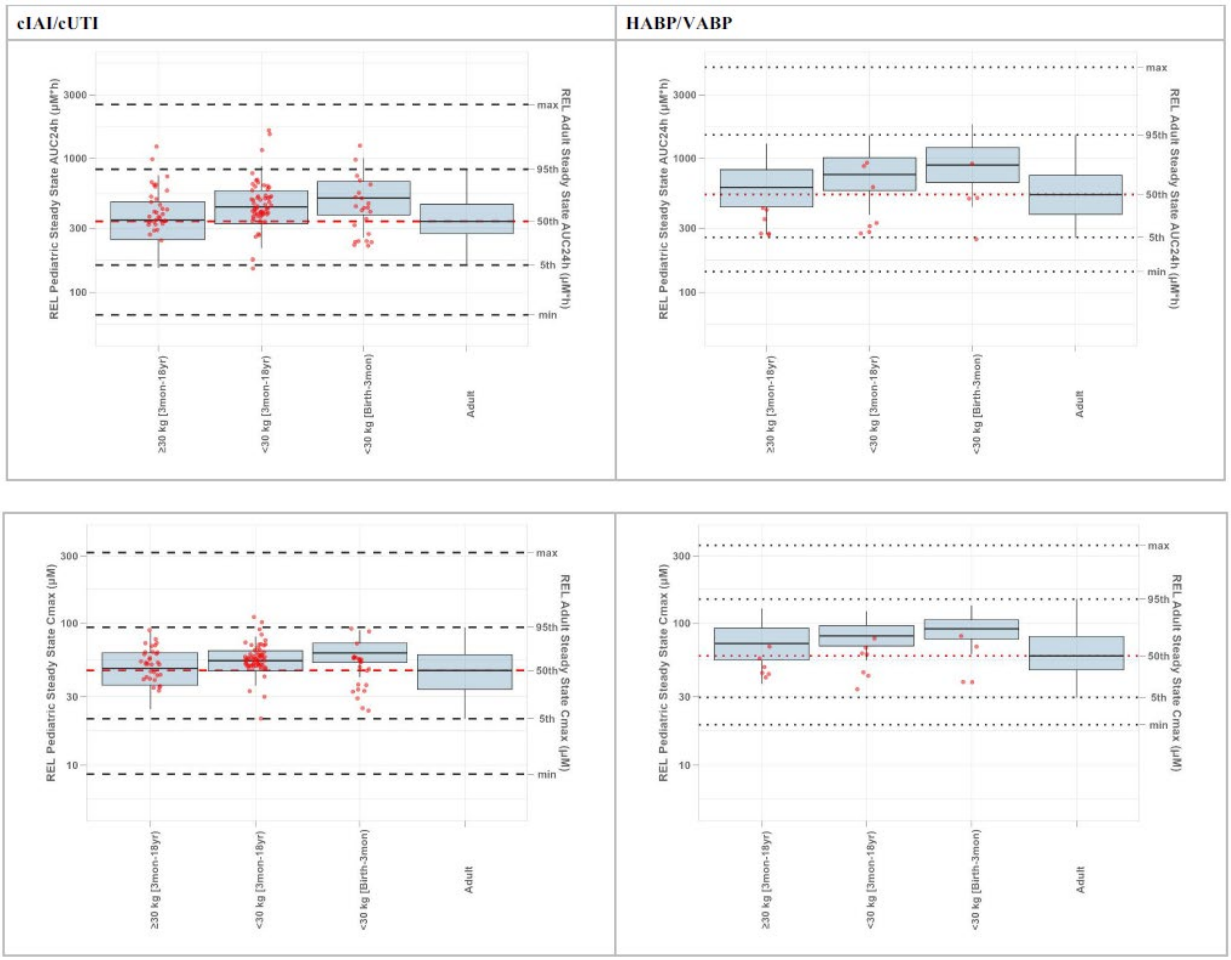
Weight-Based Dosage for Pediatric Patients ≤ 30 kg with Normal Renal Function
The proposed weight-based dosing regimen in pediatric patients weighing ≤ 30 kg with normal renal function achieved imipenem and relebactam AUC and Cmax comparable to those observed in adults with normal renal function (Figure 1 and Figure 2). When the infusion duration is extended to 60 minutes, pediatric patients <30 kg maintain Cmax values that align with the median adult values and remain within the adult 95th percentile range.

Figure 1. Comparison of Imipenem Final Pediatric Population PK Model-Predicted Steady-State Exposures (AUC0-24h [Top] and Cmax [Bottom]) Between Virtual Pediatric Population Following Administration of Recommended IMI-REL Dosing Regimen Administration and Studied Pediatric Patients and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI-REL Dosing Regimen Administration for Normal Renal Function



Notes: Boxplots represent the simulated pediatric exposures from the population PK; the blue area represents the interquartile interval; the thick black line corresponds to the median; and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Data beyond the end of the whiskers are called "outlying" points and are not plotted. Horizontal dashed and dotted lines represent the distribution of adult exposures for cIAI/cUTI and HABP/VABP, respectively. Adult exposures are the population PK-predicted exposures from Phase 2/3 studies. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. Red circles represent individual post hoc exposures in pediatric patients from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type. Left and right panels show cIAI/cUTI and HABP/VABP, respectively. Abbreviations: $AUC_{0\text{-}24h}$=area under the plasma concentration-time curve from time zero to 24 hours; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; Cmax=maximum concentration; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI=imipenem/cilastatin; IMI/REL=imipenem/cilastatin/relebactam combination; max=maximum; min=minimum.
Source: Applicant's population PK report 08pwp8, Table 28, pages 118-119.

Figure 2. Comparison of REL Final Pediatric Population PK Model-Predicted Steady-State Exposures (AUC0-24h [Top] and Cmax [Bottom]) Between Virtual Pediatric Population Following Administration of Recommended IMI-REL Dosing Regimen Administration and Studied Pediatric Patients and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI-REL Dosing Regimen Administration for Normal Renal Function



Notes: Boxplots represent the simulated pediatric exposures from the population PK model; the blue area represents the interquartile interval; the thick black line corresponds to the median; and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Data beyond the end of the whiskers are called "outlying" points and are not plotted. Horizontal dashed and dotted lines represent the distribution of adult exposures for cIAI/cUTI and HABP/VABP, respectively. Adult exposures are the PPK-predicted exposures from Phase 2/3 studies. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. Red circles represent individual post hoc exposures in pediatric patients from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type. Left and right panels show cIAI/cUTI and HABP/VABP, respectively.

Abbreviations: $AUC_{0\text{-}24h}$=area under the plasma concentration-time curve from time zero to 24 hours; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; C_{max}=maximum concentration; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI/REL=imipenem/cilastatin/relebactam combination; max=maximum; min=minimum. .

Source: Applicant's population PK report 08pwp8, Table 29, pages 120-121.

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

Yes, dose adjustments are required for pediatric patients ≥30 kg with any degree of renal impairment based on estimated glomerular filtration rate categories, as outlined in Table 13. Proposed Dosage for Adult and Pediatric (Weighing at Least 30 kg) with Renal Impairment. For patients on hemodialysis, IMI-REL should be administered after dialysis since both active components are substantially removed during the procedure.

Table 13. Proposed Dosage for Adult and Pediatric (Weighing at Least 30 kg) with Renal Impairment

Estimated Renal Function eGFR [mL/min/1.73 m^2]	Recommended Dosage of imipenem/cilastatin and relebactam) (mg)	Dosing Interval
60 to 89	1 gram (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	Every 6 hours
30 to 59	0.75 grams (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	Every 6 hours
15 to 29	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours
End Stage Renal Disease (ESRD) on Hemodialysis	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours

- Administer by IV over 30 minutes.
- Administration should be timed to follow hemodialysis.

Source: applicant's proposed USPI

Pediatric Patients ≥30 kg with Renal Impairment

Dose adjustment are proposed for pediatric patients ≥30 kg and <18 years of age across all levels of renal impairment (mild to ESRD) based on population PK modeling and simulation.

Population PK model simulations demonstrated that pediatric patients ≥30 kg with mild moderate and severe renal impairment achieved comparable imipenem and relebactam AUC and Cmax with the proposed dose adjustments compared to exposures obtained in adults with normal renal function.

Pediatric patients with ESRD (eGFR <15 mL/min/1.73m²) showed higher drug exposures compared to both adults with normal renal function and pediatric patients with eGFR ≥15 mL/min/1.73m². However, this finding is consistent with the expected pattern observed in adult patients with severe renal impairment.

When comparing ESRD patients to patients with normal renal function within each age group, both adult and pediatric populations showed increased drug exposure with similar magnitude.

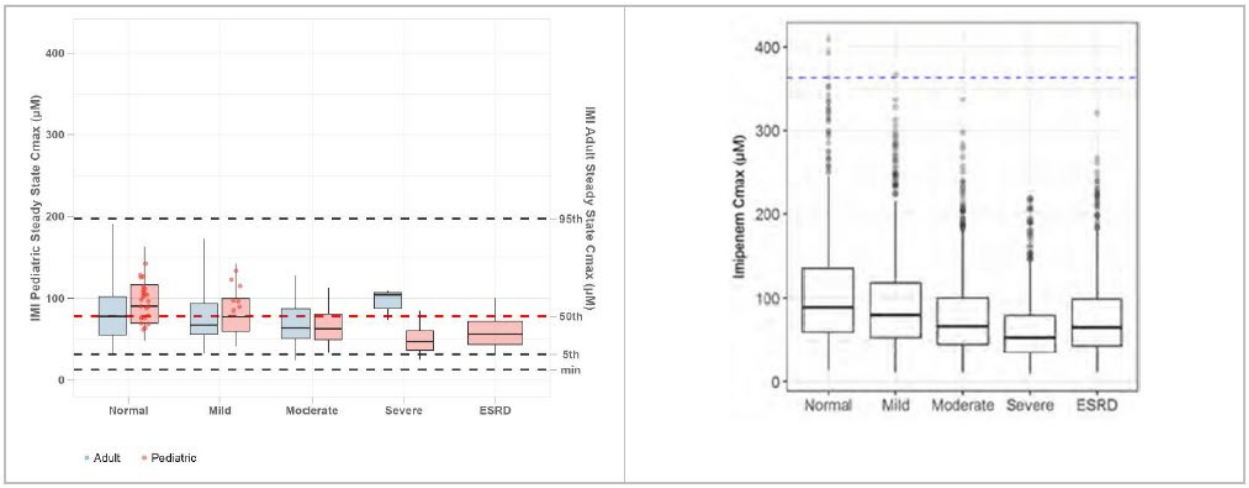
- Adults with ESRD: Approximately 40% higher imipenem exposure and 150% higher relebactam exposure compared to adults with normal renal function.
- Pediatric patients with ESRD: Approximately 30% higher imipenem exposure and 120% higher relebactam exposure compared to pediatric patients with normal renal function

The AUC and Cmax in pediatric patients (≥30 kg and <18 years of age) with an eGFR < 15 mL/min/1.73m² remain within the distribution of exposures observed in adult patients with normal renal function for both imipenem and relebactam, for whom efficacy and an acceptable safety profile have been established.

Therefore, the proposed dose adjustment in pediatric patients (≥30 kg) with renal impairment are supported by the modeling data and are clinically appropriate.

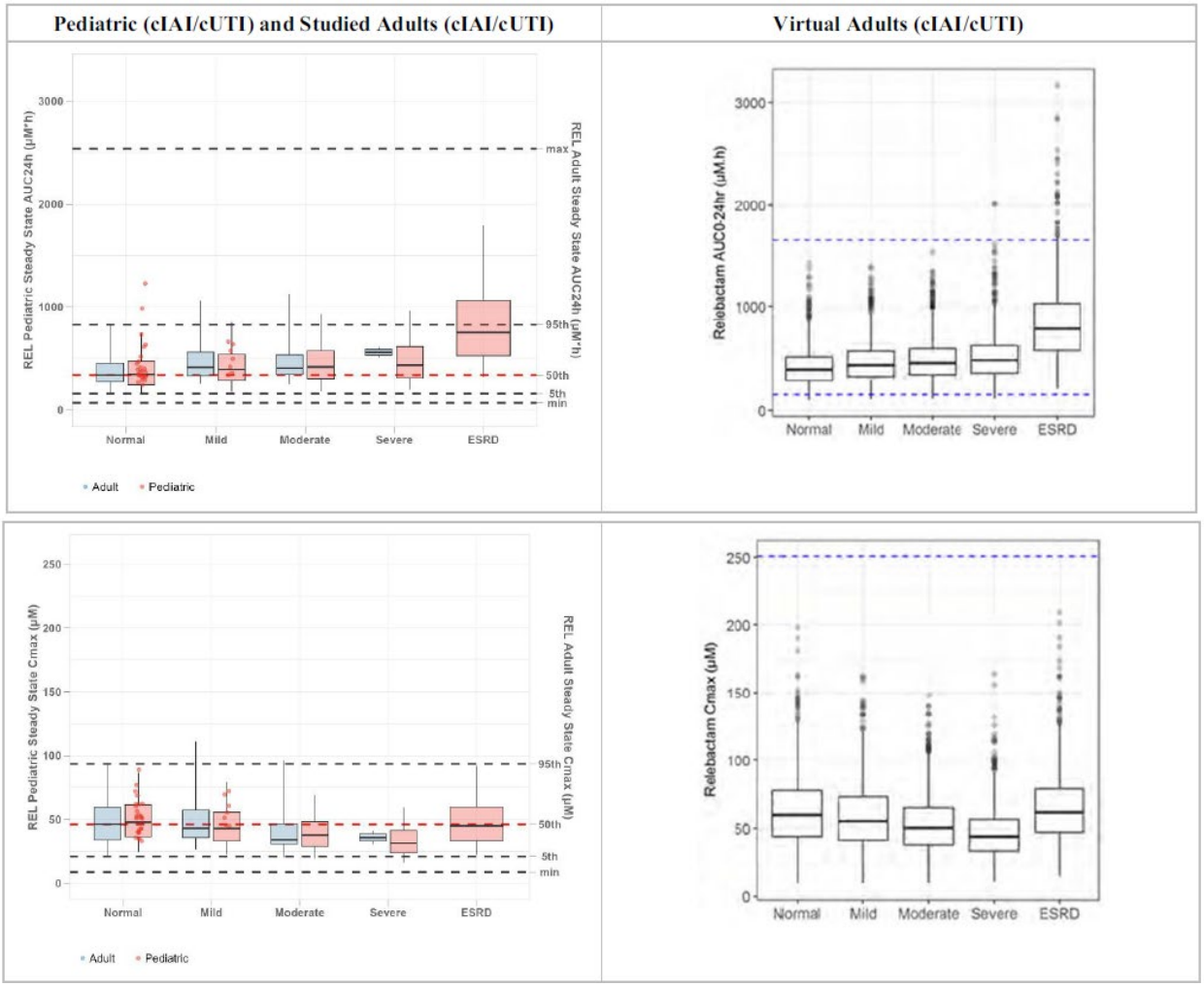
This finding is demonstrated in Figure 3 and Figure 4. The red box plots represent the simulated IMI and REL exposures for virtual pediatric patients with ESRD, which remain below the maximum exposure levels (black horizontal lines) observed in adults with normal renal function. Simulated pediatric ESRD exposures also fall within the clinical bounds of exposure in a virtual adult population (blue horizontal dashed lines in the white box plot) that was created to validate exposure distributions expected in a large adult population with renal impairment. Thus, despite showing higher exposures compared to pediatric patients with normal renal function, these elevated levels in pediatric ESRD patients do not exceed the clinically established exposure range established in the adult population.

Figure 3. Comparison of Model-Simulated and EBE-Based Post-hoc Imipenem Steady-State PK Exposures (AUC0-24h in Top Panel; Cmax in Bottom Panel) Between cIAI/cUTI Pediatric Renal Impairment Population (≥30 kg and < 18 Years of Age) and cIAI /cUTI Adult RI Population



Notes: Red box plots represent simulated virtual RI pediatric exposures using N=3155 virtual pediatric population received recommended renal function adjusted IMI-REL dosing regimen; red circles represent individual post-hoc exposures in studied pediatric patients (P020 and P021) following the protocol-defined dosing regimen; blue box plots represent individual post-hoc exposures obtained from studied adult patients receiving approved renal function adjusted IMI-REL dosing regimen; white boxplots represent simulated virtual cIAI/cUTI RI adult exposures using N=1000 virtual adult population receiving approved renal function adjusted IMI-REL dosing regimen; For these boxplots the area represents the interquartile interval, the thick black line represents median, and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Data beyond the end of the whiskers are called “outlying” points. Horizontal dashed and dotted lines in the left panels represent corresponding distribution of the studied adult post-hoc exposures from Phase 2/3 studies for cIAI/cUTI. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. The blue horizontal dashed lines in the right panels represent the upper and lower clinical bound of exposure as determined in the adult analysis.
Source: Applicant’s response to Information Request (SDN 622), Figure 3, pages 9 - 10.

Figure 4. Comparison of Model-Simulated and EBE-Based Post-hoc REL Steady-State PK Exposures (AUC0-24h in Top Panel; Cmax in Bottom Panel) Between cIAI/cUTI Pediatric Renal Impairment Population (≥30 kg and < 18 Years of Age) and cIAI /cUTI Adult RI Population



Notes: Red box plots represent simulated virtual RI pediatric exposures using N=3155 virtual pediatric population received recommended renal function adjusted IMI-REL dosing regimen; red circles represent individual post-hoc exposures in studied pediatric patients (P020 and P021) following the protocol-defined dosing regimen; blue box plots represent individual post-hoc exposures obtained from studied adult patients receiving approved renal function adjusted IMI/REL dosing regimen; white boxplots represent simulated virtual cUTI/cIAI RI adult exposures using N=1000 virtual adult population receiving approved renal function adjusted IMI-REL dosing regimen; For these boxplots the area represents the interquartile interval, the thick black line represents median, and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Data beyond the end of the whiskers are called "outlying" points. Horizontal dashed and dotted lines in the left panels represent corresponding distribution of the studied adult post-hoc exposures from Phase 2/3 studies for cIAI/cUTI. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. The blue horizontal dashed lines in the right panels represent the upper and lower clinical bound of exposure as determined in the adult analysis.
Source: Applicant's response to Information Request (SDN 622), Figure 4, pages 11 - 12.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No clinically relevant drug-drug interactions have been identified for imipenem/cilastatin/relebactam. Clinical studies in healthy adult subjects demonstrated no

drug-drug interactions among the three components of the fixed-dose combination. Additionally, concomitant administration of imipenem/cilastatin/relebactam with probenecid (an OAT3 inhibitor) did not result in clinically significant changes in imipenem or relebactam pharmacokinetics in adults. The drug interaction profile established in adults is expected to apply to pediatric patients given the comparable pharmacokinetic characteristics and elimination pathways between age groups.

Evaluation of food-drug interactions was not needed for this intravenous product.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 14. Clinical trials relevant to NDA 212819 Supplement 8 (IMI-REL, RECARBRIO)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
P021	NCT03969901	Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study	Relebactam, imipenem, cilastatin 250/500/500 mg by IV infusion: Age Cohort 1 (12 to <18yrs): 500/250 mg q6h Age Cohort 2 (6 to <12 yrs): 15/7.5 mg/kg q6h Age Cohort 3 (2 to <6 yrs): 15/7.5 mg/kg q6h Age Cohort 4 (3 mos to <2 yrs): 15/7.5 mg/kg q6h Age Cohort 5 (birth to < 3 mos): 15/7.5 mg/kg q8h All administered as 60-minute infusions Active control treatment per primary investigators	Primary: Adverse events (AEs), IV study intervention discontinuations due to AEs Secondary: All-cause mortality, Favorable clinical response, Favorable microbiological response	cIAI and cUTI: Total duration of all study intervention: Minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days; HABP/VABP: Minimum 7 days up to a	113	Birth to < 18 years of age	35 centers in 18 countries

					maximum of 14 days.			
		Other studies pertinent to the review of efficacy or safety						
P020	NCT03230916	Phase 1b, Open-label, Single-dose Study	Initial: relebactam, imipenem, cilastatin 250/500/500 mg by IV infusion: Age Cohort 1 (12 to <18yrs): 15/7.5 mg/kg over 30 min Age Cohort 2 (6 to <12 yrs): 15/7.5 mg/kg over 30 min Age Cohort 3 (2 to <6 yrs): 15/7.5 mg/kg over 30 min Age Cohort 4 (3 mos to <2 yrs): 10/5 mg/kg over 60 min Age Cohort 5 (birth to < 3 mos): 10/5 mg/kg over 60 min Modified: relebactam, imipenem, cilastatin 250/500/500 mg by IV infusion: Age Cohort 1 (12 to <18yrs): 250/500/500 mg over 30 min Age Cohort 2 (6 to <12 yrs): 15/7.5 mg/kg over 60 min Age Cohort 3 (2 to <6 yrs): 15/7.5 mg/kg over 60 min Age Cohort 4 (3 mos to <2 yrs): 15/7.5 mg/kg over 60 min Age Cohort 5 (birth to < 3	Characterize the pharmacokinetic profile of relebactam, imipenem, cilastatin	Single dose with 14 day follow-up	46	Birth to < 18 years of age	21 centers in 8 countries

			mos): 15/7.5 mg/kg over 60 min					

Source: Clinical reviewer.

7.2. Review Strategy

The efficacy to support the cUTI, cIAI and HABP/VABP indications in pediatrics is extrapolated from studies conducted in adults. Therefore, the pediatric studies were designed with relatively small sample sizes to primarily evaluate pharmacokinetics, safety and tolerability. Efficacy results were assessed descriptively and no formal hypothesis testing was performed. The clinical trial data submitted were from a PK study in 5 age cohorts that resulted in modification of the initial dosing proposal that was subsequently utilized in the clinical study involving the 5 age cohorts in patients with cUTI, cIAI and HABP/VABP.

Data sources reviewed included protocols, statistical analysis plans, study reports, patient-level datasets, and case report forms. The SDTM and ADaM datasets are available at the following location in the Agency's Electronic Document Room: \\CDSESUB1\EVSPROD\nda212819\0601\

The quality of submitted data was sufficient for review purposes. The protocols and statistical analysis plans were sufficiently informative and comprehensive, and the Applicant's reported analyses were consistent with planned analyses.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study P021

Trial Design

Study P021 (Study P021MK7655A, clinicaltrials.gov identifier: NCT03969901) was a phase 2/3 open-label, randomized, multisite, active-controlled study designed to assess the safety, tolerability, efficacy and PK of IMI/REL in pediatric participants from birth to less than 18 years of age with confirmed or suspected gram-negative bacterial infections. The study randomized participants from 35 centers in 15 countries.

Participants were stratified by age group and infection type prior to randomization. The five pediatric age groups evaluated in the study were:

1. Adolescents (12 to <18 years)
2. Older children (6 to <12 years)
3. Younger children (2 to <6 years)
4. Infants and toddlers (3 months to < 2years)
5. Neonates and young infants (birth to <3 months)

Eligible participants included males or females from birth to less than 18 years of age who required hospitalization and treatment with IV antibacterial therapy for confirmed or suspected gram-negative bacterial infection (in the absence of meningitis) including HABP/VABP, cUTI, or cIAI. Individuals were excluded from the study if they met any of the following exclusion criteria:

- Were expected to survive less than 72 hours.
- Had a concurrent infection that would interfere with evaluation of response to the study antibacterial agents (IMI/REL or Active Control), including any of the following: endocarditis, osteomyelitis, meningitis, prosthetic joint infection, active pulmonary tuberculosis, or a disseminated fungal infection.
- Had a concomitant infection at the time of randomization that required non-study systemic antibacterial agent therapy in addition to IV study intervention or oral stepdown therapy (medications with only gram-positive activity [e.g., vancomycin, linezolid] were allowed).
- Had HABP/VABP caused by an obstructive process, including lung cancer or other known obstruction.
- Had a cUTI that met any of the following criteria:
    - Complete obstruction of any portion of the urinary tract
    - Documented reflux of ileal loop urinary diversion
    - Suspected or confirmed perinephric or intrarenal abscess
    - Suspected or confirmed prostatitis, urethritis, or epididymitis
    - Trauma to pelvis/urinary tract
    - Presence of indwelling urinary catheter that could not be removed at study entry
- Had any of the following medical conditions at screening:
    - A history of a seizure disorder
    - Cystic fibrosis

- If less than 3 months of age, had received more than 72 hours of empiric antibacterial agent treatment for suspected meningitis prior to initiation of IV study intervention.
- If 3 months of age or older, or <3 months without suspected meningitis, had received potentially therapeutic antibacterial agent therapy (e.g., with gram-negative activity), including bladder infusions with topical urinary antiseptics or antibacterial agents, for a duration of more than 24 hours during the 48 hours preceding the first dose of study intervention.
- Had an estimated CrCl (based on the Cockcroft-Gault equation, for participants ≥12 years of age) or estimated glomerular filtration rate (eGFR, based on the modified Schwartz equation, for participants <12 years of age) below that specified for the appropriate age range; or requires peritoneal dialysis, hemodialysis, or hemofiltration.
- Had ALT or AST ≥5 x ULN at the time of screening.

Participants were randomized in a 3:1 ratio to receive IMI/REL or active control. The route of administration for IMI/REL was intravenous infusion. For IV infusion the dosage level of IMI/REL was

- Age cohort 1: 500/250 mg q6h.
- Age cohort 2: 15/7.5 mg/kg q6h.
- Age cohort 3: 15/7.5 mg/kg q6h.
- Age cohort 4: 15/7.5 mg/kg q6h.
- Age cohort 5: 15/7.5 mg/kg q8h.

The IMI/REL duration was

- CIAI and cUTI: Total duration of all study intervention is minimum 5 days (IV alone or IV then oral, of which at least 3 days must be IV alone before optional oral switch) up to a maximum of 14 days.
- HABP/VABP: Minimum 7 days up to a maximum of 14 days.

For oral switch in the IMI-REL arm, the dosages were per the investigator, summary of product characteristics, or international treatment guidelines. The active control was not standardized but chosen by the investigator based on acceptable options for each infection type.

The analysis populations consisted of the modified intent-to-treat (MITT) and the microbiological modified intent-to-treat (mMITT) populations. The MITT population included all randomized participants who received at least 1 dose of IV study intervention. Of the 115 randomized participants, 113 (98.3%) were included in the MITT population. Two randomized participants were not included in the MITT population due to withdrawal by parent/guardian.The MITT population was used for analysis of all-cause mortality through Day 28 post randomization and clinical response. Participants were included in the intervention group to which they were randomized.

The mMITT population included all randomized participants who met the following conditions:

- For participants with HABP/VABP and cIAI:
    - The participant received at least 1 dose of IV study intervention; AND
    - The participant's baseline infection-site culture grew at least 1 gram-negative pathogenic organism.
- For participants with cUTI:
    - The participant received at least 1 dose of IV study intervention; AND
    - The participant's baseline urine culture grew at least 1 gram-negative pathogenic organism at sufficient quantity (ie, growth at $\geq 10^5$ CFU/mL of uropathogen).

Of the 115 randomized participants, 90 (78.3%) were included in the mMITT population. Twenty-three randomized participants (20.0%) had a baseline culture that did not meet culture identification requirements for inclusion. The mMITT population was used for analysis of clinical response and microbiological response. Participants were included in the intervention group to which they were randomized.

Study Endpoints

The primary endpoints for safety were the presence of adverse events. The primary endpoint for tolerability was IV study intervention discontinuation due to adverse events. There was no primary endpoint for efficacy.

The secondary endpoints for efficacy were all-cause mortality at day 28 post-randomization, and favorable clinical and overall microbiological response at the end of therapy (EOT), early follow up (EFU, 7 to 14 days after EOT) and late follow-up (LFU, 7 to 14 days after EFU). Favorable clinical response consisted of improvement, cure and sustained cure. Favorable overall microbiological response consisted of presumed eradication and eradication.

The secondary endpoints for PK were plasma concentration of imipenem and relebactam, $AUC_{0\text{-}24hr}$ abd C_{eoi} for imipenem and relebactam, and %*f*T>MIC for imipenem.

Statistical MethodsThis was an estimation study; no formal hypothesis test was performed for any endpoint. The planned overall enrollment for P021 was 115 participants across 5 age cohorts. All efficacy endpoints were binary and within-group 95% confidence intervals were calculated using the Agresti & Coull method. 95% confidence intervals for between-treatment differences in the incidence (or percentage of participants) were calculated using the unstratified Miettinen and Nurminen method.

Safety and tolerability were assessed by clinical review of all safety assessments, including AEs (including protocol-defined ECIs) laboratory tests, and vital signs. The analysis of safety results followed a tiered approach.

Sparse PK sampling was performed during the IV study intervention period and the individual participants plasma concentration-time data for imipenem, cilastatin, and REL were reported.

An interim review of aggregated safety and tolerability data was conducted by an independent external data monitoring committee (eDMC) for Age Cohorts 1, 2, and 3. This review was performed when each of Age Cohorts 2 and 3 had at least 20 participants in the safety population with complete data available (all complete data available from Age Cohorts 1, 2, and 3 were reviewed). This was used to assess the overall safety and tolerability profiles and confirm dosing regimens for Age Cohorts 4 and 5.

In addition to the eDMC interim review of safety and tolerability data, an internal interim review of complete separate and aggregated safety, tolerability, efficacy, and PK data from Age Cohorts 1 through 3 was performed prior to enrollment of Age Cohorts 4 and 5. This internal interim review was conducted independently from the eDMC interim review, but considered any critical safety findings from the eDMC assessment. Results were reviewed by an internal team to assess whether the safety, tolerability, efficacy, and PK were acceptable for each age cohort. The findings from the internal interim review were considered during dose selection and supported the decision to confirm the proposed doses for Age

Cohorts 4 and 5. Based on the interim review, no changes were necessary to dosing regimens for any of the age cohorts.

Protocol Amendments

The original protocol was issued on November 19, 2018. There were 5 amendments, among which 3 were global.

In amendment 2, on August 27, 2019, the overall planned enrollment number was decreased from 140 participants across 5 age cohorts to 115 participants across 5 age cohorts based on an interim review of the safety and PK data. The planned enrollment numbers by age group and by infection site were also decreased. Slower than anticipated enrollment into Age Cohorts 4 and 5 prompted a reevaluation of the planned sample size from ≥28 participants to ≥20 participants in Age Cohort 4, and from ≥28 participants to ≥8 participants in Age Cohort 5. Moreover, the percentage of participants with cIAI having a diagnosis other than complicated appendicitis was modified from ≥10% of participants to ≥9% of participants.

Decreasing enrollment to 115 participants did not negatively impact the key goals or scientific validity of the studies and allowed for sufficient data to evaluate safety, efficacy, and PK in both intervention groups. This sample size was also determined to be sufficient to support identification of dosing regimens in the targeted pediatric population.

8.1.2. Study Results

Compliance with Good Clinical Practices

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

Patient Disposition

One hundred and thirty participants were enrolled in the study, of which 115 were randomized. The safety and treated analysis sets contain 113 participants each. The MITT analysis population, used for evaluating the clinical response, consists of 113 participants. The mMITT analysis population, used for evaluating the microbiological response, consists of 90 participants. Study P021 analysis populations are summarized in the table below.

Table 15. Analysis Populations, Study P021

Analysis Set	Total N (%)
Enrolled	130
Randomized	115
Treated	113
Safety	113

MITT	113
mMITT	90

Abbreviations: MITT, modified intent-to-treat; mMITT, microbiological modified intent-to-treat
Source: Statistical reviewer analysis; adsl.xpt

In the randomized analysis set, 29 participants were assigned to the active control arm and 86 to the IMI/REL arm. In the active control arm, 28 participants were treated and all of them completed the study. The participant that discontinued the study was withdrawn by parent/guardian. 23 participants completed the treatment; among the 5 participants who discontinued the treatment, 2 discontinued due to an adverse event, 2 discontinued due to a decision by the physician and 1 discontinued for an unstated reason.

In the IMI-REL arm, 85 participants were treated and 84 completed the study. The two participants that discontinued the study were withdrawn by parent/guardian. 72 participants completed the treatment; among the 13 participants who discontinued the treatment, 4 discontinued due to an adverse event, 2 discontinued due to a decision by the physician, 1 was withdrawn by parent/guardian and 6 discontinued for an unstated reason. Study P021 participant disposition is summarized in the table below.

Table 16. Participant Disposition, Randomized Participants, Study P021

Disposition	**IMI-REL N=86**	**Active Control N=29**	**Total N=115**
Treated	85 (0.99)	28 (0.97)	113 (0.98)
Completed Treatment	72 (0.84)	23 (0.79)	95 (0.83)
Discontinued Treatment	13 (0.15)	5 (0.17)	18 (0.16)
Completed Study	84 (0.98)	28 (0.97)	112 (0.97)
Discontinued Study	2 (0.02)	1 (0.03)	3 (0.03)

Abbreviations: IMI/REL, imipenem/cilastatin/relebactam
Source: Statistical reviewer Analysis; adsl.xpt

Protocol Violations/Deviations

The planned overall enrollment was approximately 140 participants across 5 age cohorts. In Amendment 2, it was reduced to 115 participants across 5 age cohorts due to slower than anticipated enrollment into cohorts 4 and 5. Accrued safety and PK data from across the pediatric clinical development program were found to be sufficient to characterize the safety and PK profiles of IMI-REL in participants aged 0 to <2 years.

Demographic and Other Baseline Characteristics

Table below summarizes demographic and baseline characteristics of subjects in the randomized participants. Sex, ethnicity and race did not have any significant imbalance between the two arms. Only 6 participants had HABP/VABP (1 participant in the active control arm and 5 participants in the IMI-REL arm). Only 11 participants were in the age group Birth to <3 Months (3 participant in the active control arm and 8 participants in the IMI/REL arm).

Table 17. Demographic and Baseline Characteristics, Randomized Participants, Study P021

	IMI-REL N=86	Active Control N=29	Total N=115
Sex, n (%)			
Male	43 (50)	16 (55)	59 (51)
Female	43 (50)	13 (45)	56 (49)
Ethnicity, n (%)			
Hispanic or Latino	34 (40)	9 (31)	43 (37)
Not Hispanic or Latino	50 (58)	20 (69)	70 (61)
Not Reported	2 (2)	0 (0)	2 (2)
Race, n (%)			
American Indian or Alaska Native	3 (3)	1 (3)	4 (3)
Asian	0 (0)	1 (3)	1 (1)
Black or African American	3 (3)	1 (3)	4 (3)
White	72 (84)	22 (76)	94 (82)
Multiple	8 (9)	4 (14)	12 (10)
Infection site, n (%)			
cIAI	40 (47)	14 (48)	54 (47)
cUTI	41 (48)	14 (48)	55 (48)
HABP/VABP	5 (6)	1 (3)	6 (5)
Age group, n (%)			
Birth to <3 Months	8 (9)	3 (10)	11 (10)
3 Months to <2 Years	15 (17)	5 (17)	20 (17)
2 to <6 Years	22 (26)	8 (28)	30 (26)
6 to <12 Years	31 (36)	11 (38)	42 (37)
12 to <18 Years	10 (12)	2 (7)	12 (10)
Age (years)			
Mean (SD)	5.9 (4.8)	5.5 (4.5)	5.8 (4.7)
Median	5.0	5.0	5.0
IQR	1.8, 9.0	1.8, 8.0	1.8, 9.0
Min, Max	0, 17	0, 17	0, 17

Abbreviations: IMI/REL, imipenem/cilastatin/relebactam; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; VABP, hospital-acquired bacterial pneumonia
Source: Statistical reviewer analysis; adsl.xpt

Treatment Compliance and Prior and Concomitant Medications

Study intervention compliance was high (>95%) and generally comparable for both intervention groups across infection type. IV study intervention compliance in the MITT population was consistent with the All Randomized population across infection type.

Most participants in the MITT population (97.3%) had received at least 1 prior medication; the rate was comparable for both intervention groups (97.6% for the IMI/REL group and 96.4% for the Active Control group). Most participants (87.6%) received at least 1 concomitant medication; the rate was comparable for both intervention groups (87.1% for the IMI/REL group and 87.6% for the Active Control group). The frequency of reported prior and concomitant medications (including anti-infective medications) were generally comparable for both the IMI/REL and Active Control groups.

Efficacy Results – Primary Endpoint

There were no primary endpoints for efficacy.

Data Quality and Integrity

Data quality was sufficient for review purposes. There were no study site inspections for this application.

Efficacy Results – Secondary and other relevant endpoints

No participant died in either intervention group in the study through Day 28.
The majority of participants in the MITT population (>69% in both intervention groups) achieved a favorable clinical response at the EOT, EFU, and LFU visits (Table 18). The percentage of participants who achieved a favorable clinical response at the EOT, EFU, and LFU visits was comparable for the IMI/REL and Active Control groups.

Table 18. Analysis of clinical response by visit, all infection types (MITT)

Visit	Clinical Response	IMI-REL	Active Control	Difference
EOT	Favorable	67/85 (68.9, 86.2)[1]	21/28 (56.4, 87.6)[1]	3.8 (-12.3, 23.9)[2]
	Cure	57/85 (56.5, 76.1)[1]	20/28 (52.8, 84.9)[1]	-4.4 (-21.9, 16.5)[2]
	Improvement	10/85 (6.3, 20.5)[1]	1/28 (0, 19.2)[1]	8.2 (-6.8, 17.7)[2]
	Unfavorable	18/85 (13.8, 31.1)[1]	7/28 (12.4, 43.6)[1]	-3.8 (-23.9, 12.3)[2]
	Failure	1/85 (0, 7)[1]	0/28 (0, 14.3)[1]	1.2 (-11, 6.4)[2]
	Indeterminate	17/85 (12.8, 29.8)[1]	7/28 (12.4, 43.6)[1]	-5 (-25, 11)[2]
EFU	Favorable	60/85 (60.1, 79.3)[1]	21/28 (56.4, 87.6)[1]	-4.4 (-21.1, 16.1)[2]
	Sustained Cure	53/85 (51.7, 71.9)[1]	20/28 (52.8, 84.9)[1]	-9.1 (-26.7, 12)[2]
	Cure	7/85 (3.8, 16.3)[1]	1/28 (0, 19.2)[1]	4.7 (-10.1, 13.4)[2]
	Unfavorable	25/85 (20.7, 39.9)[1]	7/28 (12.4, 43.6)[1]	4.4 (-16.1, 21.1)[2]
	Relapse	4/85 (1.5, 11.9)[1]	0/28 (0, 14.3)[1]	4.7 (-7.6, 11.5)[2]
	Failure	1/85 (0, 7)[1]	0/28 (0, 14.3)[1]	1.2 (-11, 6.4)[2]
	Indeterminate	20/85 (15.7, 33.6)[1]	7/28 (12.4, 43.6)[1]	-1.5 (-21.7, 14.8)[2]
LFU	Favorable	59/85 (58.9, 78.2)[1]	21/28 (56.4, 87.6)[1]	-5.6 (-22.3, 15)[2]
	Sustained Cure	57/85 (56.5, 76.1)[1]	21/28 (56.4, 87.6)[1]	-7.9 (-24.7, 12.8)[2]
	Cure	2/85 (0.1, 8.7)[1]	0/28 (0, 14.3)[1]	2.4 (-9.9, 8.2)[2]
	Unfavorable	26/85 (21.8, 41.1)[1]	7/28 (12.4, 43.6)[1]	5.6 (-15, 22.3)[2]
	Relapse	4/85 (1.5, 11.9)[1]	0/28 (0, 14.3)[1]	4.7 (-7.6, 11.5)[2]
	Failure	1/85 (0, 7)[1]	0/28 (0, 14.3)[1]	1.2 (-11, 6.4)[2]

	Indeterminate	21/85 (16.7, 34.9)[1]	7/28 (12.4, 43.6)[1]	-0.3 (-20.6, 16.1)[2]

Abbreviations: MITT, modified intent-to-treat; IMI/REL, imipenem/cilastatin/relebactam; EOT, end of therapy; EFU, early follow-up; LFU, late follow-up
1. 95% confidence interval via the Agresti-Coull method
2. 95% confidence interval via the Miettinen-Nurminen method
Source: Statistical reviewer analysis; adeff.xpt

The percentage of participants who achieved a favorable clinical response at the EFU visits was comparable for the IMI/REL and Active Control groups across the three infection sites and the five ages cohorts is presented in the tables below.

Table 19. Analysis of Clinical Response at EFU by Infection site, MITT Population, Study P021

Infection Site	Clinical Response	IMI-REL	Active Control	Difference
HABP/ VABP	Favorable	5/5 (51.1, 100)[1]	1/1 (16.7, 100)[1]	0 (-48, 82.2)[2]
	Sustained Cure	5/5 (51.1, 100)[1]	1/1 (16.7, 100)[1]	0 (-48, 82.2)[2]
cIAI	Favorable	34/39 (72.8, 94.9)[1]	13/14 (66.5, 100)[1]	-5.7 (-21.7, 20.2)[2]
	Sustained Cure	30/39 (61.5, 87.6)[1]	12/14 (58.8, 97.2)[1]	-8.8 (-28.5, 19.5)[2]
	Cure	4/39 (3.5, 24.2)[1]	1/14 (0, 33.5)[1]	3.1 (-22.5, 18.5)[2]
	Unfavorable	5/39 (5.1, 27.2)[1]	1/14 (0, 33.5)[1]	5.7 (-20.2, 21.7)[2]
	Relapse	1/39 (0, 14.4)[1]	0/14 (0, 25.1)[1]	2.6 (-19.5, 13.3)[2]
	Indeterminate	4/39 (3.5, 24.2)[1]	1/14 (0, 33.5)[1]	3.1 (-22.5, 18.5)[2]
cUTI	Favorable	21/41 (36.5, 65.7)[1]	7/13 (29.1, 76.8)[1]	-2.6 (-31.1, 27.1)[2]
	Sustained Cure	18/41 (29.9, 59)[1]	7/13 (29.1, 76.8)[1]	-9.9 (-38.2, 19.9)[2]
	Cure	3/41 (1.8, 20.1)[1]	0/13 (0, 26.6)[1]	7.3 (-16.3, 19.6)[2]
	Unfavorable	20/41 (34.3, 63.5)[1]	6/13 (23.2, 70.9)[1]	2.6 (-27.1, 31.1)[2]
	Relapse	3/41 (1.8, 20.1)[1]	0/13 (0, 26.6)[1]	7.3 (-16.3, 19.6)[2]
	Failure	1/41 (0, 13.7)[1]	0/13 (0, 26.6)[1]	2.4 (-20.9, 12.7)[2]
	Indeterminate	16/41 (25.6, 54.3)[1]	6/13 (23.2, 70.9)[1]	-7.1 (-36.4, 21.4)[2]

Abbreviations: EFU, early follow-up; MITT, modified intent-to-treat; IMI/REL, imipenem/cilastatin/relebactam; HABP, hospital-acquired bacterial pneumonia; VABP, hospital-acquired bacterial pneumoniacIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection;
1. 95% confidence interval via the Agresti-Coull method
2. 95% confidence interval via the Miettinen-Nurminen method
Source: Statistical reviewer Analysis; adeff.xpt

Table 20. Analysis of Clinical Response at EFU by Age Cohort, all Infection Types, mMITT Population, Study P021

Age Cohort	Overall Microbiological Response	IMI-REL	Active Control	Difference
1	Favorable	9/10 (57.4, 100)[1]	1/2 (9.5, 90.5)[1]	40 (-13.4, 85.1)[2]
	Sustained Cure	8/10 (47.9, 95.4)[1]	1/2 (9.5, 90.5)[1]	30 (-26, 78.4)[2]
	Cure	1/10 (0, 42.6)[1]	0/2 (0, 71)[1]	10 (-60.1, 41.9)[2]
	Unfavorable	1/10 (0, 42.6)[1]	1/2 (9.5, 90.5)[1]	-40 (-85.1, 13.4)[2]
	Indeterminate	1/10 (0, 42.6)[1]	1/2 (9.5, 90.5)[1]	-40 (-85.1, 13.4)[2]
2	Favorable	24/31 (59.9, 88.9)[1]	9/11 (51.2, 96)[1]	-4.4 (-27.6, 28.3)[2]
	Sustained Cure	20/31 (46.9, 79)[1]	8/11 (42.9, 90.8)[1]	-8.2 (-34.8, 25.6)[2]
	Cure	4/31 (4.5, 29.5)[1]	1/11 (0, 39.9)[1]	3.8 (-26.7, 22.6)[2]
	Unfavorable	7/31 (11.1, 40.1)[1]	2/11 (4, 48.8)[1]	4.4 (-28.3, 27.6)[2]
	Indeterminate	7/31 (11.1, 40.1)[1]	2/11 (4, 48.8)[1]	4.4 (-28.3, 27.6)[2]
3	Favorable	18/21 (64.5, 95.9)[1]	7/8 (50.8, 99.9)[1]	-1.8 (-26.4, 35.6)[2]
	Sustained Cure	16/21 (54.5, 89.8)[1]	7/8 (50.8, 99.9)[1]	-11.3 (-37.2, 27.3)[2]
	Cure	2/21 (1.4, 30.1)[1]	0/8 (0, 37.2)[1]	9.5 (-24.8, 29.3)[2]
	Unfavorable	3/21 (4.1, 35.5)[1]	1/8 (0.1, 49.2)[1]	1.8 (-35.6, 26.4)[2]
	Relapse	1/21 (0, 24.4)[1]	0/8 (0, 37.2)[1]	4.8 (-29, 23.1)[2]
	Indeterminate	2/21 (1.4, 30.1)[1]	1/8 (0.1, 49.2)[1]	-3 (-39.7, 20.4)[2]
4	Favorable	4/15 (10.5, 52.4)[1]	3/4 (28.9, 96.6)[1]	-48.3 (-78.7, 5.4)[2]
	Sustained Cure	4/15 (10.5, 52.4)[1]	3/4 (28.9, 96.6)[1]	-48.3 (-78.7, 5.4)[2]
	Unfavorable	11/15 (47.6, 89.5)[1]	1/4 (3.4, 71.1)[1]	48.3 (-5.4, 78.7)[2]
	Relapse	3/15 (6.3, 46)[1]	0/4 (0, 54.6)[1]	20 (-33.4, 45.9)[2]
	Failure	1/15 (0, 31.8)[1]	0/4 (0, 54.6)[1]	6.7 (-44.8, 30.6)[2]
	Indeterminate	7/15 (24.8, 69.9)[1]	1/4 (3.4, 71.1)[1]	21.7 (-31.8, 57.3)[2]
5	Favorable	5/8 (30.4, 86.5)[1]	1/3 (5.6, 79.8)[1]	29.2 (-33.3, 72.7)[2]
	Sustained Cure	5/8 (30.4, 86.5)[1]	1/3 (5.6, 79.8)[1]	29.2 (-33.3, 72.7)[2]
	Unfavorable	3/8 (13.5, 69.6)[1]	2/3 (20.2, 94.4)[1]	-29.2 (-72.7, 33.3)[2]
	Indeterminate	3/8 (13.5, 69.6)[1]	2/3 (20.2, 94.4)[1]	-29.2 (-72.7, 33.3)[2]

Abbreviations: EFU, early follow-up; mMITT, microbiological modified intent-to-treat; IMI/REL, imipenem/cilastatin/relebactam;
1. 95% confidence interval via the Agresti-Coull method
2. 95% confidence interval via the Miettinen-Nurminen method
Source: Statistical reviewer Analysis; adeff.xpt

Most participants in the mMITT population (>85% in both intervention groups) achieved a favorable microbiological response at the EOT, EFU, and LFU visits (see the table below). The percentage of participants who achieved a favorable microbiological response at the EOT, EFU, and LFU visit was comparable for the IMI/REL and Active Control groups.

Table 21. Analysis of Overall Microbiological Response by Visit, all Infection Types, mMITT Population, Study P021

Visit	Overall Microbiological Response	IMI-REL	Active Control	Difference
EOT	Favorable	65/68 (87.3, 99)[1]	20/22 (71, 98.7)[1]	4.7 (-5.6, 23.9)[2]
	Unfavorable	3/68 (1, 12.7)[1]	2/22 (1.3, 29)[1]	-4.7 (-23.9, 5.6)[2]
	Indeterminate	3/68 (1, 12.7)[1]	2/22 (1.3, 29)[1]	-4.7 (-23.9, 5.6)[2]
EFU	Favorable	58/68 (74.8, 92)[1]	20/22 (71, 98.7)[1]	-5.6 (-18.5, 14.4)[2]
	Unfavorable	10/68 (8, 25.2)[1]	2/22 (1.3, 29)[1]	5.6 (-14.4, 18.5)[2]
	Indeterminate	5/68 (2.8, 16.5)[1]	2/22 (1.3, 29)[1]	-1.7 (-21.2, 9.5)[2]
LFU	Favorable	59/68 (76.5, 93.1)[1]	19/22 (65.8, 96.1)[1]	0.4 (-13.5, 21.3)[2]
	Unfavorable	9/68 (6.9, 23.5)[1]	3/22 (3.9, 34.2)[1]	-0.4 (-21.3, 13.5)[2]
	Indeterminate	6/68 (3.8, 18.3)[1]	2/22 (1.3, 29)[1]	-0.3 (-19.8, 11.4)[2]

Abbreviations: mMITT, microbiological modified intent-to-treat; IMI/REL, imipenem/cilastatin/relebactam; EOT, end of therapy; EFU, early follow-up; LFU, late follow-up
1. 95% confidence interval via the Agresti-Coull method
2. 95% confidence interval via the Miettinen-Nurminen method
Source: Satistical reviewer analysis; adeff.xpt

The majority of participants in the mMITT population (>79%, in both intervention groups) achieved a favorable clinical response at the EOT, EFU, and LFU visits. The percentage of participants who achieved a favorable clinical response at the EOT, EFU, and LFU visits was comparable for the IMI-REL and Active Control groups.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

There is only one trial submitted in support of the safety, tolerability, efficacy and PK of IMI-RELin pediatric participants with confirmed or suspected gram-negative bacterial infection. Therefore, no integrated assessment of efficacy across trials was performed.

8.1.4. Integrated Assessment of Effectiveness

A single non-comparative study 7655A-021 was conducted to provide information regarding the safety, tolerability, efficacy and PK of IMI-REL in pediatric participants with confirmed or suspected gram-negative bacterial infection. This trial was considered acceptable since the causative pathogens, course of disease, and approach to treatment are similar in adult and pediatric patients. Therefore, achievement of comparable exposures to adult patients is expected to result in similar efficacy in pediatric patients allowing for extrapolation of efficacy to the pediatric population from the adult data.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of RECARBRIO in adults was previously assessed in the original NDA for the treatment

of cUTI, cIAI and HABP/VABP. The current safety review in pediatric patients is based on the safety findings from the two studies of IMI-REL performed in participants from birth to less than 18 years of age: P020, a single dose, pharmacokinetic study in 5 age groups, and P021, a phase 2/3 open-label, randomized, active-controlled, multicenter study of cUTI, cIAI and HABP/VABP. Since study P020 was a single-dose, non-comparative, open-label study aimed at evaluating PK and safety, only a summary of safety data from study P020 is included in this review (see Section 8.2.8).

8.2.2. Review of the Safety Database

Overall Exposure

In total, 131 pediatric patients were exposed to IMI-REL in the P020 (46 patients) and P021 studies (85 patients). A total of 28 patients received the comparator active control. The median age of IMI-REL exposed patients in the P021 study was 5 years. The median duration of threapy with IMI-REL for cUTI, cIAI, and HABP/VABP was 5, 6, and 13 days, respectively. Table 22 provides information on the exposure for each infection type by infection type and age cohort. Table 23 below provides information on the dosage regimens utilized in Study P021 based on age group.

Table 22. Exposure to RECARBRIO by infection and age cohort

	Patients exposed to IMI-REL (n=85)		
Age group	**cUTI**	**cIAI**	**HABP/VABP**
Age Cohort 1 (12 to <18 years)	4	5	1
Age Cohort 2 (6 to <12 years)	10	21	0
Age Cohort 3 (2 to <6 years)	6	14	2
Age Cohort 4 (3 months to <2 years)	14	0	1
Age Cohort 5 (birth to <3 months)	7	0	1
Total	**41**	**40**	**5**

Source: Clinical reviewer

Table 23. Dosage Regiments of RECARBRIO in Study 21

Age group	**Doses**
Age Cohort 1 (12 to <18 years, n=10)	500/250mg q6 hours
Age Cohort 2 (6 to <12 years, n=31)	15/7.5mg/kg q6 hours
Age Cohort 3 (2 to <6 years, n=21)	15/7.5mg/kg q6 hours
Age Cohort 4 (3 months to <2 years, n=15)	15/7.5mg/kg q6 hours
Age Cohort 5 (birth to <3 months, n=8)	15/7.5mg/kg q8 hours
Total	**85**

Source: Clinical reviewer

Adequacy of the safety database:

The safety database was adequate in terms of the size and population distribution. Safety

evaluations included vital signs, routine physical examination, and laboratory tests. Patients were monitored for adverse events. Events of clinical interest (elevated liver enzymes meeting specific criteria) were identified and recorded.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

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

Categorization of Adverse Events

The severity of AEs was assessed as follows:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
- Severe: An event that prevents normal everyday activities (for pediatric studies, extremely distressed or unable to do usual activities).

Routine Clinical Tests

Routine laboratory tests included White Blood Cell Count with Differential, Platelet Count, Hemoglobin, Hematocrit, Blood Urea Nitrogen, Potassium, Sodium, Bicarbonate, Chloride, Glucose, Phosphorous, Creatinine, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal), Albumin, Total Protein, Calcium, Alkaline phosphatase, Carbon dioxide, routine urinalysis and serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test (as appropriate).

8.2.4. Safety Results

Deaths

No participant died.

Serious Adverse Events

Table below summarizes adverse events reported in Study P021. 13 participants had at least one serious adverse event (the rates were comparable in the two treatment groups). Among these, 2 participants had at least one serious drug-related adverse event (the rates were comparable in the two treatment groups), 2 discontinued drug due to a serious adverse event (the rates were comparable in the two treatment groups), and 1 discontinued drug due to a serious drug-related AE (the rates were comparable in the two treatment groups).

Table 24. Adverse Event Summary During Therapy and 14-Day Follow-up Period, All Participants as Treated, Study P021

AE type	IMI-REL N=85	Active Control N=28	Difference
with one or more AEs	57 (56.5, 76.1)[1]	14 (32.6, 67.4)[1]	17.1 (-3.5, 37.2)[2]
with drug-related AEs	17 (12.8, 29.8)[1]	5 (7.4, 36.1)[1]	2.1 (-17.2, 16.6)[2]
from IV therapy	16 (11.8, 28.5)[1]	5 (7.4, 36.1)[1]	1 (-18.3, 15.3)[2]
from oral step-down therapy	1 (0, 7)[1]	0 (0, 14.3)[1]	1.2 (-11, 6.4)[2]
with serious AEs	10 (6.3, 20.5)[1]	3 (2.9, 28)[1]	1.1 (-16.4, 12.5)[2]
with serious drug-related AEs	2 (0.1, 8.7)[1]	0 (0, 14.3)[1]	2.4 (-9.9, 8.2)[2]
from IV therapy	1 (0, 7)[1]	0 (0, 14.3)[1]	1.2 (-11, 6.4)[2]
from oral step-down therapy	1 (0, 7)[1]	0 (0, 14.3)[1]	1.2 (-11, 6.4)[2]
who died	0 (0, 5.2)[1]	0 (0, 14.3)[1]	0 (-12.2, 4.4)[2]
discontinued drug due to an AE	5 (2.2, 13.4)[1]	2 (0.9, 23.7)[1]	-1.3 (-17.3, 7.8)[2]
discontinued IV therapy	3 (0.8, 10.3)[1]	0 (0, 14.3)[1]	3.5 (-8.7, 9.9)[2]
discontinued oral step-down therapy	2 (0.1, 8.7)[1]	2 (0.9, 23.7)[1]	-4.8 (-20.6, 2.8)[2]
discontinued drug due to a drug-related AE	3 (0.8, 10.3)[1]	0 (0, 14.3)[1]	3.5 (-8.7, 9.9)[2]
discontinued IV therapy	2 (0.1, 8.7)[1]	0 (0, 14.3)[1]	2.4 (-9.9, 8.2)[2]
discontinued oral step-down therapy	1 (0, 7)[1]	0 (0, 14.3)[1]	1.2 (-11, 6.4)[2]
discontinued drug due to a serious AE	2 (0.1, 8.7)[1]	2 (0.9, 23.7)[1]	-4.8 (-20.6, 2.8)[2]
discontinued IV therapy	0 (0, 5.2)[1]	0 (0, 14.3)[1]	0 (-12.2, 4.4)[2]
discontinued oral step-down therapy	2 (0.1, 8.7)[1]	2 (0.9, 23.7)[1]	-4.8 (-20.6, 2.8)[2]
discontinued drug due to a serious drug-related AE	1 (0, 7)[1]	0 (0, 14.3)[1]	1.2 (-11, 6.4)[2]
discontinued IV therapy	0 (0, 5.2)[1]	0 (0, 14.3)[1]	0 (-12.2, 4.4)[2]
discontinued oral step-down therapy	1 (0, 7)[1]	0 (0, 14.3)[1]	1.2 (-11, 6.4)[2]

Abbreviations: AE, adverse event; IMI-REL, imipenem/cilastatin/relebactam
1. 95% confidence interval via the Agresti-Coull method
2. 95% confidence interval via the Miettinen-Nurminen method
Source: Satistical reviewer analysis; adae.xpt

Dropouts and/or Discontinuations Due to Adverse Effects

There were 3 participants that discontinued IMI-REL due to adverse events. Two participants developed rash (Patients (b) (6) and (b) (6)) and both adverse events were considered related to IMI-REL by the investigator. Patient (b) (6) was an 11-year-old male that developed the rash on day 5 of treatment and study drug was stopped; the rash resolved by day 11 and he completed the study. Patient (b) (6) was an 8-year-old male who developed a rash on day 3 that lasted 15 minutes and resolved without apparent intervention. He completed the study on alternate medications. The other patient was a 3-month-old male with left arm swelling due to IV infusion leakage on day 3; he was discharged on oral antibacterials and the swelling resolved on day 6. This was not considered related to IMI-REL.

Reviewer comment: Although patient (b) (6) was felt to have a drug-related rash by the investigator, the duration and rapid spontaneous resolution are unusual and this may not be actually drug-related, as location and character of rash are not described.

Significant Adverse Events

Elevated liver enzymes or potential drug-induced liver injury events meeting specific criteria were predefined in the protocol as Events of Clinical Interest (ECI). No ECIs were reported in the study.

Treatment Emergent Adverse Events and Adverse Reactions

Fifty-seven (67%) participants in the IMI-REL group had TEAEs compared with 14 (50%) in the active control group (see Table 25). The proportion of patients with severe and serious TEAEs was similar between treatment groups: 9 (11%) and 10 (12%) in IMI-REL vs 3 (11%) and 3 (11%) in active control, respectively. Drug discontinuations due to TEAEs were also similar and there were no deaths. The majority of TEAEs were mild or moderate in severity. Table 26 summarizes TEAEs observed in Study P021 by age cohort. Table 27 displays the most common TEAEs, which were vomiting, diarrhea, nausea, headache, phlebitis/infusion site reactions, and rash.

Table 25. Summary of TEAEs by Severity in Study P021

AE category	IMI-REL	Active Control
	(N=85)	(N=28)
	n (%)	n (%)
Any TEAE	57 (67.1)	14 (50.0)
Any serious TEAE	10 (11.8)	3 (10.7)
Any severe TEAE	9 (10.6)	3 (10.7)
Any drug discontinuation due to TEAE	5 (5.9)	2 (7.1)
IV drug discontinuation due to TEAE	3 (3.5)	0
Deaths due to TEAE	0	0

Abbreviations: TEAE, treatment emergent adverse e; IV, intravenous
Source: Clinical reviewer analysis.

Table 26. Summary of Subjects with TEAEs by System Organ Class Stratified by Age Cohort

	Cohort 1 (12 to <18 years)		Cohort 2 (6 to <12 years)		Cohort 3 (2 to <6 years)		Cohort 4 (3 months to <2 years)		Cohort 5 (Birth to <3 months)		Total	
	IMI-REL	Active Control	IMI-REL	Active Control	IMI-REL	Active Control	IMI-REL	Active Control	IMI-REL	Active Control	IMI-REL	Active Control
	(N=10)	(N=2)	(N=31)	(N=11)	(N=21)	(N=8)	(N=15)	(N=4)	(N=8)	(N=3)	(N=85)	(N=28)
Any AE	6 (60.0)	1 (50.0)	20 (64.5)	4 (36.4)	15 (71.4)	5 (62.5)	14 (93.3)	2 (50.0)	2 (25.0)	2 (66.7)	57 (67.1)	14 (50.0)
System Organ Class												
Gastrointestinal disorders	2 (20.0)	0	14 (45.2)	2 (18.2)	7 (33.3)	4 (50.0)	2 (13.3)	0	1 (12.5)	0	26 (30.6)	6 (21.4)
General disorders and administration site conditions	3 (30.0)	1 (50.0)	6 (19.4)	1 (9.1)	2 (9.5)	2 (25.0)	3 (20.0)	0	0	0	14 (16.5)	4 (14.3)
Infections and infestations	1 (10.0)	0	3 (9.7)	2 (18.2)	2 (9.5)	1 (12.5)	7 (46.7)	1 (25.0)	0	2 (66.7)	13 (15.3)	6 (21.4)
Blood and lymphatic system disorders	0	0	2 (6.5)	0	5 (23.8)	0	3 (20.0)	1 (25.0)	0	1 (33.3)	10 (11.8)	2 (7.1)
Investigations	0	0	4 (12.9)	0	2 (9.5)	1 (12.5)	2 (13.3)	0	0	0	8 (9.4)	1 (3.6)
Nervous system disorders	3 (30.0)	0	3 (9.7)	0	1 (4.8)	0	0	0	0	0	7 (8.2)	0
Skin and subcutaneous tissue disorders	2 (20.0)	0	2 (6.5)	0	1 (4.8)	1 (12.5)	1 (6.7)	0	0	0	6 (7.1)	1 (3.6)
Musculoskeletal and connective tissue disorders	1 (10.0)	0	0	0	2 (9.5)	0	1 (6.7)	0	0	0	4 (4.7)	0
Renal and urinary disorders	0	0	1 (3.2)	0	0	0	2 (13.3)	0	1 (12.5)	0	4 (4.7)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (3.2)	0	2 (9.5)	0	1 (6.7)	0	0	0	4 (4.7)	0
Vascular disorders	0	0	1 (3.2)	0	3 (14.3)	0	0	0	0	0	4 (4.7)	0
Eye disorders	1 (10.0)	0	1 (3.2)	0	1 (4.8)	0	0	0	0	0	3 (3.5)	0

Metabolism and nutrition disorders	0	0	1 (3.2)	0	0	2 (25.0)	1 (6.7)	0	0	0	2 (2.4)	2 (7.1)
Reproductive system and breast disorders	0	0	0	0	1 (4.8)	0	1 (6.7)	0	0	0	2 (2.4)	0
Cardiac disorders	0	0	0	0	0	2 (25.0)	0	0	1 (12.5)	0	1 (1.2)	2 (7.1)
Injury, poisoning and procedural complications	0	0	1 (3.2)	0	0	0	0	0	0	0	1 (1.2)	0

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: TRTFL = 'Y'; Column Variable 1: AGECOHT (Age Cohort); Column Variable 2: TRT01A (Actual Treatment for Period 01).
Any AE - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'.
System Organ Class Preferred Term - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Row Variable 1: AEBODSYS (Body System or Organ Class); Row Variable 2: AEDECOD (Dictionary-Derived Term).

Table 27. Adverse Reactions Occurring in Greater Than or Equal to 3% of Pediatric Patients Receiving RECARBRIO vs Active Control in Study P021

Adverse Reaction	IMI-REL	Active control
	(N=85)	(N=28)
	N (%)	N (%)
Gastrointestinal disorders		
Vomiting	13 (15%)	3 (11%)
Diarrhea	8 (9%)	2 (7%)
Nausea	6 (7%)	2 (7%)
General disorders and administration site conditions		
Phlebitis/Infusion site reactions*	4 (5%)	2 (7%)
Nervous system disorders		
Headache	5 (6%)	0
Skin and subcutaneous tissue disorders		
Rash	3 (4%)	0

*Phlebitis/Infusion site reactions includes phlebitis, infusion site phlebitis, infusion site extravasation, and medical device site dermatitis
**Rash includes rash, rash erythematous, and rash maculopapular.

Laboratory Findings

For study P021, 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.

Vital Signs

For the phase 2/3 study P021, 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)

There were no ECG findings reported in studies P020/P021 .

QT

QT was not measured in studies P020 and P021.

Immunogenicity

Immunogenicity was not assessed in this supplement.

8.2.5. Analysis of Submission-Specific Safety Issues

Elevated liver enzymes or potential drug-induced liver injury events meeting specific criteria were predefined in the protocol as Events of Clinical Interest (ECI). No ECIs were reported in the study.

8.2.6. Clinical Outcome Assessment (COA)

Clinical outcome in Study P021 was assessed by clinician as described in Section 8.1 of this review.

8.2.7. Safety Analyses by Demographic Subgroups

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

8.2.8. Adverse Events in Study P020

In study P020, 8/46 (17%) participants experienced at least 1 AE. Of these participants, 7 had AEs that were mild in intensity, and 1 participant had an AE categorized as severe in intensity (anemia/thrombocytosis). All reported AEs occurred in the posttreatment period, and none led to infusion interruption/discontinuation or study discontinuation. The AE profile was generally comparable between Cohorts 1 to 3 and Cohorts 4 and 5, indicating no difference in safety profile across age groups. There were no SAEs or deaths reported during the study. Overall, the most frequently reported AEs were anemia (6.5%) and diarrhea (6.5%).

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new carcinogenicity studies were submitted. The original NDA found that the components of IMI-REL were not found to have mutagenic potential. 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 studies of IMI-REL in pediatric patients in excluded patients who were pregnant or breastfeeding.

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

IMI-REL and its components are not known to be associated with abuse, withdrawal or rebound effects. It is typically administered in a hospital setting making the possibility of overdose less likely. No overdoses occurred in the pediatric studies P020 and P021.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Review of the post-marketing safety reports did not reveal any new safety issues related to use in pediatric patients. There was a report of a 12-year-old patient who started therapy with IMI-REL on an unknown date for "pseudomonas infection" (off-label use in unapproved age group). There were no additional co-reported clinical AEs. The event outcome was unknown, and no additional information was provided. No new safety signals related to the use of IMI-REL in adult patients were identified in postmarketing safety reports from January 16, 2021 through July 15, 2025.

Expectations on Safety in the Postmarket Setting

RECARBRIO is currently on the market and based on review of the data in this submission, there are no expectations for the development of new safety issues if the approved indications are expanded to include pediatric patients from birth to < 18 years of age.

8.2.11. Integrated Assessment of Safety

The assessment of the safety of RECARBRIO for the treatment of cUTI, cIAI and HABP/VABP in pediatric patients from birth to less than 18 years of age is based on the 131 patients that were enrolled in clinical studies P020 and P021. The overall incidence of AEs with patients who received RECARBRIO were comparable with those who received the active comparator. The majority of TEAEs were mild or moderate in severity. There were no SAEs that resulted in study drug discontinuation. There were no potential Hy's Law cases. No deaths were reported. Also, no clinically significant changes in vital signs, physical examination findings, or laboratory results were reported. The overall safety profile of RECARBRIO in pediatric patients from birth to less than 18 years of age was similar to the safety profile in adults with cUTI, cIAI and HABP/VABP treated with RECARBRIO. No new safety signals were identified.

8.3. Statistical Issues

No formal hypothesis testing was conducted. The number of participants with HABP/VABP (1 participant in the active control arm and 5 participants in the IMI/REL arm) and the number of participants in the age group Birth to <3 Months (3 participant in the active control arm and 8 participants in the IMI/REL arm) were small, so any conclusion drawn from the data for these two subgroups must be viewed with caution.

8.4. Conclusions and Recommendations

The clinical and statistical reviewers conclude that the Applicant has submitted adequate evidence to support the safety and effectiveness of RECARBRIO in pediatric patients from birth to < 18 years of age for the treatment of cUTI (in patients with limited or no alternative treatment options), cIAI (in patients with limited or no alternative treatment options), and HABP/VABP. The determination of the

effectiveness of RECARBRIO in the treatment of cUTI, cIAI and HABP/VABP in pediatric patients is extrapolated from the clinical experience of RECARBRIO in the treatment of adults with cUTI, cIAI and HABP/VABP. The assessment of the safety of RECARBRIO in the treatment of cUTI, cIAI and HABP/VABP is based on data from the pediatric clinical study P021 and the PK study P020. The overall safety profile of RECARBRIO in pediatric patients from birth to less than 18 years of age was similar to the safety profile in adults treated with RECARBRIO for cUTI, cIAI and HABP/VABP, and no new safety signals were identified.

9 Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting convened for this sNDA.

10 Pediatrics

The current submission addresses the safety and efficacy of RECARBRIO in the treatment of cUTI, cIAI and HABP/VABP in pediatric patients from birth to <18 years. The FDA Pediatric Review Committee (PeRC) was consulted and agrees this application fulfills PREA PMR 3865-1. There are no outstanding PMRs. The Division of Pediatric and Maternal Health (DPMH) was consulted for assistance with the review of pediatric labeling language included in the Prescribing Information (PI). DPMH participated in applicable team meetings to discuss the application and proposed labeling recommendations.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved). The finalized PI was compared to the currently approved PI and the Applicant's draft PI submitted and received on February 13, 2025 (see Table 28 below).

The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 28. Major Labeling Changes with the Rationale for the Changes

Full Prescribing Information (FPI) Sections[1,3]	**Applicant Proposed Labeling**	**Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI) [2]**
1 INDICATIONS AND USAGE	Replaced the age group statement "(b) (4)" with adult and pediatric patients " in the indication statements for HABP/VABP, cUTI and cIAI in subsections 1.1, 1.2 and 1.3, respectively, of the PI.	Revised the proposed age group statement to read as "adult and pediatric patients weighing at least 2 kg." This weight threshold was added because dosing is not proposed for approval in pediatric patients weighing less than 2 kg. In Subsection 1.4 (Limitations of Use) added the following statements: RECARBRIO is not recommended in pediatric patients less than 37 weeks post-menstrual age (gestational age at birth plus post-natal age) *[see Dosage and Administration (2.2) and Use in Specific Populations (8.4)]*. RECARBRIO is not recommended in pediatric patients weighing less than 30 kg with renal impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)]*. These limitations of use statements are also added to the Dosage and Administration section. Refer to Section 6 of this Summary Review and, the Division of Pediatric and Maternal Health review in DARRTS dated 11/24/2025) for additional information.

2 DOSAGE AND ADMINISTRATION[3]	In subsection (b) (4) revised the header and text for recommended dosage in adult patients to include pediatric patients weighing at least 30 kg.	Removed pediatric dosage and administration information from subsection (b) (4) and moved it to subsection 2.2 so that all pediatric dosage and administration nformation are conveyed under the same subsection heading.
	In subsection 2.2, added header, text and table for the recommended dosage in pediatric patients weighing less than 30 kg with normal renal function.	Revised header to read as "Recommended Dosage in Pediatric Patients weighing at least 2 kg" in subsection 2.2.
	The added pediatric dosage table is based on body weight (2kg to less than 30 kg) and age (birth to less than 18 years old. This table was also added to the Highlights section of the PI.	Revised the pediatric dosage table to add dosage and administration information for pediatric patients weighing 30 kg or greater, in subsection 2.2. Added the the following footnote to make it clear that this refers to at least 37 weeks post-menstrual age "Pediatric patients from birth (includes pediatric patients at least 37 weeks post-menstrual age)."
	The individual doses of each active ingredient were included next to the Recarbrio in the pediatric dosage table.	The individual doses of each active ingredient added as footnotes to improve readability of doses in the table and avoid dosing confusion for health care providers.
	In subsection 2.2, added the following statement: (b) (4) RECARBRIO is not recommended in pediatric patients weighing less than 30 kg with renal impairment, pediatric patients (b) (4) (less than 37 weeks post-menstrual age)."	Added a statement that "RECARBRIO is not recommended in pediatric patients less than 37 weeks post-menstrual age (gestational age at birth plus post-natal age*) [see Indications and Usage (1.4) and Use in Specific Populations (8.4)]."*
	Subsection 2.3 on dosage adjustment in patients with renal impairment was revised to include (b) (4)	In (b) (4) subsection 2.4 where renal impairment dosing is provided for pediatric patients weighing at least 30 kg. Subsection 2.3 is retitled to "Recommended Dosage in Adult Patients with Renal Impairment."

		In the table in subsection 2.3, replaced the term (b) (4) with range of values for renal function. Subsection 2.4, titled "Recommended Dosage in Pediatric Patients Weighing at Least 30 kg with Renal Impairment" was created including a separate table with dosing instructions. The statement proposed by the Applicant " (b) (4) "was replaced with the statement "Calculated using a GFR estimating equation validated in pediatric patients weighing at least 30 kg ." These changes were based on the labeling recommendations in the FDA Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products-Content and Format (2023) at https://www.fda.gov/media/72142/download Please refer to the Division of Pediatric and Maternal Health review in DARRTS dated 11/24/2025, Section 6 of this Multi-disciplinary Review for additional details that support the rationale for the changes, and to the RECARBRIO prescribing information for additional details on the finalized labeling language.
5 WARNINGS AND PRECAUTIONS[3]	Text under the Hypersensitivity Reactions section in the Warnings and Precautions (W&P) section in the Highlights (HL), section of the PI states (b) (4) ."	Revised (b) (4) at the beginning of the statement in the W&P section of the HL to read as "Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta lactam drugs" to align with the current wording in the W&P section of the FPI to avoid minimizing the risk as per the OPDP recommendations (see OPDP review dated 11/04/2025 in DARRTS).
6 ADVERSE REACTIONS[3]	In the Highlights section of the PI, the following bullet is added to the Adverse Reactions section: Pediatric HABP/VABP, cUTI, or cIAI Patients: (b) (4)	Adverse Reactions section in the Highlights section of the PI is revised to: Pediatric HABP/VABP, cUTI, and cIAI Patients: The most common adverse reactions occurring in greater than 3% of pediatric patients receiving RECARBRIO were vomiting, diarrhea, nausea, headache, phlebitis/infusion site reactions, and rash.

	In the FPI, Section 6 , Adverse Reactions, Subsection 6.1 Clinical Trial Experience, Pediatric Patients subheading is added where adverse events reported in the phase 2/3 clinical study of RECARBRIO in pediatric participants from birth to less than 18 years of age are described under the title, "Clinical Trial Experience in Pediatric Patients with HABP/VABP, cUTI and cIAI."	Subsection 6.1 Clinical Trial Experience, Pediatric Patients subheading is revised to include weight-based dosing used in the pediatric study and to revise the threshold for the most common adverse reactions to >3%, along with additional editorial changes. Please refer to the Section 8 of this Multi-disciplinary Review for additional details that support the rationale for the changes and the RECARBRIO prescribing information for the finalized labeling language.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.4 Pediatric Use subsection: (b) (4) The safety profile of RECARBRIO in pediatric patients (b) (4) *[see Adverse Reactions (6.1)]*.	To distinguish data supporting use in pediatric population for HABP/VABP vs cUTI/cIAI, 8.4 Pediatric Use subsection is revised to: The safety and effectiveness of RECARBRIO for the treatment of HABP/VABP, and for the treatment of cUTI and cIAI in patients who have limited or no alternative treatment options have been established in pediatric patients weighing at least 2 kg. Use of RECARBRIO in pediatric patients is supported by evidence from an adequate and well-controlled trial of RECARBRIO in adults with HABP/VABP, controlled trials in adults with cUTI and cIAI, and additional pharmacokinetic and efficacy data from pediatric trials *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1,14.2 and 14.3)]*. The safety profile of RECARBRIO in pediatric patients from the pediatric trials was comparable to that in adults treated with RECARBRIO *[see Adverse Reactions (6.1)]*.

	(b) (4)	RECARBRIO is not recommended in pediatric patients less than 37 weeks post-menstrual age (gestational age at birth plus post-natal age) or weighing less than 30 kg with renal impairment. The safety and effectiveness of RECARBRIO for the treatment of HABP/VABP, cUTI or cIAI have not been established in pediatric patients weighing less than 2 kg. Division of Pediatric and Maternal Health review in DARRTS (dated 11/24/2025) and sections 6 and 10 of this Multi-disciplinary Review for additional information.
	8.6 Renal Impairment subsection Reduce RECARBRIO dosage in adult patients with a CLcr less than 90 mL/min and in pediatric patients weighing at least 30 kg with eGFR less than 90 mL/min/1.73 m^2 *[see Dosage and Administration (2.3, 2.5) and Clinical Pharmacology (12.3)]*. (b) (4) RECARBRIO is not recommended in pediatric patients weighing less than 30 kg with renal impairment, (b) (4)	Because the lack of data is usually not specified in labeling, 8.6 Renal Impairment subsection was revised to: Reduce RECARBRIO dosage in adult patients with a CLcr less than 90 mL/min and in pediatric patients weighing at least 30 kg with an eGFR less than 90 mL/min/1.73 m^2 *[see Dosage and Administration (2.3, 2.4) and Clinical Pharmacology (12.3)]*. RECARBRIO is not recommended in pediatric patients weighing less than 30 kg with renal impairment. Refer to section 6 of this Multi-disciplinary Review for additional details.

12 CLINICAL PHARMACOLOGY	Pediatric Patients subheading was added to 12.3 Pharmacokinetics subsection to provide information on the pharmacokinetics of imipenem and relebactam as well as to describe the need for dose adjustment based on renal function.	Pediatric Patients subheading in 12.3 Pharmacokinetics subsection was revised to summarize the pediatric clinical studies from which the data were obtained to derive steady-state PK parameters for patients with various infections following recommended pediatric dosing regimens, (b) (4). Language referencing (b) (4) was removed since this information is already included in subsection 2.3. Please refer to section 6 of this Multi-disciplinary Review for additional details that support the rationale for the changes and the RECARBRIO prescribing information for the finalized labeling language.
14 CLINICAL STUDIES	Subsection titled, "14.3 Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia (HABP/VABP), Complicated Urinary Tract Infections (cUTI), and Complicated Intra-abdominal Infections (cIAI) in Pediatric Patients" describing the results of the pediatric study was added.	The section was revised. The main revisions were related to providing clinical outcomes by infection types – clinical cure rates for HABP/VABP and cIAI and clinical cure and microbiological response for cUTI, as compared to the Applicant's proposal (b) (4). Providing clinical response by infection type was deemed more meaningful for health care providers. Please refer to section 8 of this Multi-disciplinary Review for additional details that support the rationale for the changes and the RECARBRIO prescribing information for the finalized labeling language.

[1] The product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved. The finalized PI was compared to the currently approved PI and the applicant's draft PI.

[3] The major updates to the Highlights section of the PI to the Indications and Usage, Dosage and Administration, Warnings and Precautions and Adverse Reactions sections to align with the FPI were also mentioned in the corresponding sections of the FPI column in the table.

Approved Labeling Types
Upon approval of this efficacy supplement, the following labeling document will be FDA-approved:

- Prescribing Information

12 Risk Evaluation and Mitigation Strategies (REMS)

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

13 Postmarketing Requirements and Commitment

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

14 Deputy Division Director (Clinical, designated signatory) Comments

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

15 Appendices

15.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): Studies P020 and P021

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 332		
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): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Financial disclosure information was provided for the investigators who conducted the (b) (6) . A total of 329 investigators (principal and sub-investigators) were certified regarding the absence of financial interests and/or arrangements. In (b) (6), the principal investigator and 1 sub-investigator from site (b) (6) disclosed significant payment of other sorts ($108,450.75 and $204,636.62, respectively). Both were for (b) (6) for other research studies. (b) (6) enrolled (b) (6) and it is unlikely the significant payments of other sorts reported from 2 investigators at this site will affect the overall results. (b) (6) 1 sub-investigator of site (b) (6) was not certified regarding the absence of financial interests and arrangements because the sub-investigator did not return the

form with the requested information despite multiple due diligence attempts. This lack of information is not likely to affect the overall results.

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

The bioanalytical method validation was performed for determination of imipenem, relebactam and cilastatin in plasma. Clinical studies utilized validated hydrophilic interaction (HILIC) chromatography and detected with tandem mass spectrometric detection employing a turbo ion spray (TIS) interface in the positive ion mode. The bioanalytical methods used to measure concentrations of imipenem, relebactam and cilastatin were sensitive, selective, accurate, and reproducible. Stability of analytes were demonstrated during sample processing and long-term storage.

Briefly, the bioanalytical method validation and performance, as summarized in **Table 29** met the criteria recommended in the Bioanalytical Method Validation Guidance for Industry (November 2022). Incurred sample re-analysis (ISR) was completed for all studies and acceptance criteria per FDA guidance were met. A cross-validation was performed to transfer and validate the method at a new laboratory location (b) (4) while adding some additional QC concentrations and ensuring it met the new lab's standard operating procedures (**Table 30**).

Table 29. Summary Method Performance For The Assay Used to Quantify Imipenem, Relebactam and Cilastatin for Studies P020 and P021

Study no.	BP-0005: Main Validation Report - Validation Report for the Determination of MK-7655,Cilastatin, and Imipenem in Human Plasma	
Bioanalytical matrix	Plasma	
Anticoagulant	K2EDTA (dipotassium ethylenediaminetetraacetic acid)	
Extraction methods	Protein Precipitation	
Drug	Imipenem Cilastatin Relebactam	
Internal Standard	[D5]-MK-7655 (for relebactam) [13C3, 15N]-Cilastatin (for cilastatin) [13C3, 15N2, D2]-Imipenem (for imipenem)	
Validation Range (ng/mL)	0.250 µg/mL to 100 µg/mL	
QC Levels (ng/mL)	0.75, 25, and 80 µg/mL.	
Validation Parameters	Method Validation Summary	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ Relebactam Imipenem Cilastatin	 6 6 6
	Cumulative accuracy from LLOQ to ULOQ Relebactam Cilastatin Imipenem	 98.80 to 102.00% 98.60 to 101.20% 98.00 to 101.10%
	Cumulative precision (%CV) from LLOQ to ULOQ	

	Relebactam Cilastatin Imipenem	0.79 to 4.00% 1.22 to 8.00% 1.51 to 8.00%
Performance of QCs during accuracy and precision runs	Cumulative accuracy in 6 replicates of QCs QCs for MK-7655: 0.75, 25 and 80 µg/mL QCs for Cilastatin: 0.75, 25 and 80 µg/mL QCs for Imipenem: 0.75, 25 and 80 µg/mL	 90.67 to 94.60% 92.00 to 97.96% 89.38 to 91.84%
	Inter-batch %CV QCs for MK-7655: 0.75, 25 and 80 µg/mL QCs for Cilastatin: 0.75, 25 and 80 µg/mL QCs for Imipenem: 0.75, 25 and 80 µg/mL	 4.10 to 4.93% 4.10 to 5.84% 3.20 to 5.88%
Bench-top/process stability	Autosampler stability was evaluated at the QC levels of 0.75 and 80 µg/mL after 70 hours of storage at 10ºC for Cilastatin and MK-7655 and 73 hours for Imipenem (n=5). Results met the acceptance criteria. Processed sample stability was evaluated at the QC levels of 0.75 and 80 µg/mL after 170 hours of storage at -70ºC using five independent aliquots. Results met the acceptance criteria.	
Freeze-Thaw stability	Freeze-Thaw stability was evaluated at 0.750 and 80 µg/mL (neat and diluted 1:10) QC levels (n=5). MK-7655: Established up to 4 freeze/thaw cycles at -70 °C. Recovery = 89.33 to 91.63%, CV < 4.48%. Cilastatin: Established up to 4 freeze/thaw cycles at -70 °C. Recovery = 84.00 to 94.99%, CV < 6.35%. Imipenem: Established up to 4 freeze/thaw cycles at -70 °C. Recovery = 85.33 to 90.75%, CV < 4.69%.	
Long-term storage	Long-term stability was evaluated at 0.750 and 80 µg/mL QC levels (n=5). MK-7655: Established up to 29 days at -20 °C and 1255 days at -70 °C. -20 °C Recovery = 105.19 to 106.67% -70 °C Recovery = 101.33 to 105.10% Cilastatin: Established up to 29 days at -20 °C and 1240 days at -70 °C. -20 °C Recovery = 108.13 to 109.33% -70 °C Recovery = 101.33 to 107.39% Imipenem: Established up to 29 days at -20 °C and 1240 days at -70 °C. -20 °C Recovery = 89.26 to 89.33% -70 °C Recovery = 92.41 to 93.33%	

Table 30. Partial Validation of Imipenem, Cilastatin and Relebactam

Study no.	Partial Validation for the Quantification of Relebactam, Cilastatin and Imipenem in Human Plasma by Turbo Ion Spray LC/MS/MS	
Changes in Method	Changed the initial LC conditions and Isocratic program to use two plumbing lines. • Updated the tuning procedure. • Updated the pre-run equilibration procedure	
Validation Parameters	Cross-validation performance	
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (% bias) in standard calibrators from LLOQ to ULOQ MK-7655 Cilastatin Imipenem	 -1.6 to 3.0% -1.0 to 1.0% -1.4 to 1.0%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 4 QCs MK-7655 Cilastatin Imipenem	 -11.3 to -5.4% -7.9 to -6.9% -8.6 to -6.0%
	Inter-batch % CV MK-7655 Cilastatin Imipenem	 ≤4.4% ≤3.9% ≤1.2%
Cross Validation	Thirty-four validation samples were prepared by spiking MK-7655, cilastatin, and imipenem at six concentration levels and divided into two splits. Split 1 was analyzed for MK-7655, cilastatin, and imipenem at the [redacted] (b) (4) reference laboratory). Split 2 was shipped to [redacted] (b) (4) (comparator laboratory), and analyzed. The concentrations of the cross-validation samples were blinded from the comparator laboratory. All cross-validation samples for MK-7655, Cilastatin and Imipenem were successfully analyzed at [redacted] (b) (4) and met acceptance criteria.	

15.3. Pharmacometrics Review

15.3.1. Population PK analysis

15.3.1.1. Review Summary

In general, the applicant's population PK analysis is considered acceptable for the purpose of describing description of imipenem and relebactam (REL) exposure in plasma in pediatric (birth to < 18 years) and adult patients, and description of the effects of intrinsic factor of pediatrics on imipenem and REL exposure. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

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

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

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic factors	**Pediatrics**	"RECARBRIO is a combination of imipenem, a penem antibacterial, cilastatin, a renal dehydropeptidase inhibitor, and relebactam, a betalactamase inhibitor, indicated in adult patients and pediatric patients (b) (4) for the treatment of the following infections caused by susceptible gram-negative microorganisms"	The PopPK model was updated by including pediatric data from Studies P020 and P021. The updated PopPK model has been reviewed by the reviewer and determined to be acceptable for describing and predicting imipenem and REL exposure in pediatric patients.
Derive exposure metrics for Exposure-response analyses	Cmin, Cmax, AUC0-24h		The applicant uses the final PopPK model to generate exposure metrics for imipenem and REL exposure in pediatric patients, and is considered to be acceptable.
Predict exposures for an alternative dosing regimen	**Body weight-based dosing** for pediatric patients (Table 39). Pediatric patients weighing at least 30 kg with r**enal impairment** (**Error! Reference source not found,** eGFR less than 90 mL/min/1.73 m^2**)**		Population PK analysis demonstrated statistically significant relationships between clearance (CL) and postmenstrual age (PMA), body weight, and renal function (eGFR) for both imipenem and REL. Thus, fixed dosage was selected for pediatric patients ≥ 30 kg, whereas body weight-based mg/kg dosing was selected for pediatric patients less than 30 kg. Simulation using the population PK model further supported these dosing regimens for pediatric patients. Dose adjustment is recommended for patients with renal impairment. Population PK

		analysis showed that the distributions of AUC_{0-24}, C_{max}, and C_{min} were generally similar between pediatric and adult populations across renal function categories when using the proposed dose-adjusted regimen.

15.3.1.2. Introduction

The primary objectives of applicant's analysis were to:

- To characterize the pharmacokinetics (PK) of imipenem and relebactam in pediatric participants (birth to <18 years of age) with complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), or hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) and assess the impact of covariates on imipenem and/or REL PK in pediatric participants.
- To generate Empirical Bayes estimate (EBE)-based individual PK exposures for pediatric participants.
- To compare adult exposure distributions with pediatric exposure distributions to support pediatric dosing recommendations.
- To predict steady-state imipenem and REL PK exposures for different pediatric age cohorts for probability of target attainment (PTA) analyses.
- To explore exposure-response (E-R) relationships for preselected efficacy and safety endpoints.
- To support PK exposure comparisons for the extrapolation of efficacy and bridging of safety for cIAI, cUTI, and HABP/VABP indications from adults to pediatric patients (birth to <18 years of age) with normal renal function and varying degrees of renal impairment (RI).

15.3.1.3. Model development

Data

The analyses were based on PK data from 2 pediatric studies. The study design, study population, and timing of blood samples varied among the 2 clinical studies. Brief descriptions of the studies included are presented in **Table 32**.

Table 32. Summary of Studies with PK Sampling Included in Population PK Analysis.

Protocol # & Study Type	Study Description & PK Sampling
Study P020 (Phase 1b pediatric)	Open-label, single-dose study to evaluate the PK, safety, and tolerability of a single IV dose of IMI/REL in pediatric participants from birth to <18 years of age receiving standard-of-care antibacterial therapy for treatment of a confirmed or suspected gram-negative bacterial infection. **PK Samples:** Sparse PK at 4 timepoints:

	1. First PK sample: pre-dose sample taken within 30 minutes before the start of study drug infusion. 2. Second PK sample: collected within 5 minutes after the end of study drug infusion. 3. Third PK sample: • Cohorts 1 through 4: obtained 1.5 to 2.5 hours after the start of study drug infusion. • Cohort 5: obtained 2 to 5 hours after the start of study drug infusion. 4. Fourth PK sample: • Cohorts 1 through 4: obtained 4.5 to 6 hours after the start of study drug infusion. • Cohort 5: obtained 6 to 12 hours after the start of study drug infusion.
Study P021 (Phase 2/3 Pediatric Study)	Phase 2/3 randomized, active controlled, parallel group, multisite, open-label study of IMI/REL in pediatric participants from birth to <18 years of age with confirmed or suspected gram-negative bacterial infection. **Blood PK Samples:** 1. Day 1 30 min prior to start of first dose. 2. End of first infusion (± 5 min). 3. 2 to 6 h after start of the first infusion 4. On therapy visit on Day 2 or Day 3 at 2 to 6 h after start of any infusion that day.

[*] *Source: Applicant's Studies P020 and P021 protocols.*

The NONMEM data file from the sponsor's proposed final model for analysis contained 1034 PK observations, 517 each for imipenem and REL (184 from Study P020 and 333 from Study P021), from 131 pediatric participants. **Table 33** and **Table 34** and provide summary statistics of the baseline demographic covariates in the analysis dataset. Dosing regimen for Studies P020 and P021 are described in **Table 35**.

Table 33. Summary of Baseline Demographic Continuous Covariates for Analysis

	P020 (N=46)	P021 (N=85)	Overall (N=131)
Age (years)			
Mean (SD)	4.09 (5.56)	5.87 (4.82)	5.24 (5.14)
Median [Min, Max]	0.955 [0.00548, 17.0]	5.00 [0.0603, 17.0]	3.00 [0.00548, 17.0]
Baseline weight (kg)			
Mean (SD)	17.1 (17.4)	23.1 (16.5)	21.0 (17.0)
Median [Min, Max]	8.05 [2.69, 55.0]	19.0 [2.52, 73.0]	16.0 [2.52, 73.0]
Height (cm)			
Mean (SD)	90.8 (41.9)	109 (34.3)	103 (38.0)
Median [Min, Max]	72.0 [49.0, 171]	115 [42.0, 169]	105 [42.0, 171]
Baseline BSA (m^2)			
Mean (SD)	0.628 (0.487)	0.814 (0.418)	0.749 (0.451)
Median [Min, Max]	0.377 [0.190, 1.59]	0.765 [0.160, 1.81]	0.682 [0.160, 1.81]
Serum creatinine (mg/dL)			
Mean (SD)	0.402 (0.169)	0.403 (0.174)	0.403 (0.172)
Median [Min, Max]	0.405 [0.100, 0.880]	0.380 [0.100, 0.880]	0.390 [0.100, 0.880]
Pediatric eGFR – original Schwartz (mL/min/1.73 m^2)			
Mean (SD)	131 (67.5)	162 (69.9)	151 (70.3)
Median [Min, Max]	138 [36.1, 312]	151 [56.3, 517]	147 [36.1, 517]
eGFR Modified Schwartz (mL/min/1.73 m^2)			
Mean (SD)	128 (74.3)	174 (88.2)	158 (86.1)
Median [Min, Max]	118 [36.1, 343]	151 [56.3, 658]	141 [36.1, 658]
eGFR-Bedside Schwartz (mL/min/1.73 m^2)			
Mean (SD)	105 (50.1)	125 (51.6)	118 (51.8)
Median [Min, Max]	106 [33.2, 260]	118 [51.6, 388]	114 [33.2, 388]
Gestational age (weeks)			
Mean (SD)	35.8 (0.303)	37.8 (2.85)	37.6 (2.78)
Median [Min, Max]	35.8 [35.6, 36.0]	38.6 [26.7, 41.4]	38.4 [26.7, 41.4]
Missing	44 (95.7%)	62 (72.9%)	106 (80.9%)
Postmenstrual age (weeks)			
Mean (SD)	38.0 (0.805)	73.5 (29.2)	70.7 (29.7)
Median [Min, Max]	38.0 [37.4, 38.6]	68.1 [38.3, 138]	60.2 [37.4, 138]
Missing	44 (95.7%)	62 (72.9%)	106 (80.9%)

Abbreviations: BSA=body surface area; eGFR=estimated glomerular filtration rate; Max=maximum; Min=minimum; N=number of participants; SD=standard deviation。
Source: Applicant's population PK report 08pwp8. Table 9 in page 49 and 50.

Table 34. Summary of Baseline Demographic Categorical Covariates for Analysis

	P020 (N=46)	P021 (N=85)	Overall (N=131)
Sex, N (%)			
Female	27 (58.7)	43 (50.6)	70 (53.4)
Male	19 (41.3)	42 (49.4)	61 (46.6)
Race, N (%)			
White	36 (78.3)	71 (83.5)	107 (81.7)
Black	4 (8.7)	3 (3.5)	7 (5.3)
Asian	1 (2.2)	0 (0)	1 (0.8)
Other	5 (10.9)	11 (12.9)	16 (12.2)
Ethnicity, N (%)			
Hispanic or Latino	6 (13.0)	34 (40.0)	40 (30.5)
Non-Hispanic or Latino	39 (84.8)	49 (57.6)	88 (67.2)
Unknown	1 (2.2)	2 (2.4)	3 (2.3)
Renal function based on eGFR-Bedside Schwartz, N (%)			
eGFR ≥90	29 (63.0)	76 (89.4)	105 (80.2)
eGFR [60 to <90)	7 (15.2)	7 (8.2)	14 (10.7)
eGFR [30 to <60)	10 (21.7)	2 (2.4)	12 (9.2)
eGFR [15 to <30)	0 (0)	0 (0)	0 (0)
eGFR <15	0 (0)	0 (0)	0 (0)
Ventilation status, N (%)			
Non-ventilated	0 (0)	2 (2.4)	2 (1.5)
Ventilated	0 (0)	3 (3.5)	3 (2.3)
n/a	46 (100)	0 (0)	46 (35.1)
Missing	0 (0)	80 (94.1)	80 (61.1)
Infection type, N (%)			
Healthy volunteers	0 (0)	0 (0)	0 (0)
cIAI	1 (2.2)	39 (45.9)	40 (30.5)
cUTI	16 (34.8)	41 (48.2)	57 (43.5)
HABP/VABP	12 (26.1)	5 (5.9)	17 (13.0)
Bacterial infection	7 (15.2)	0 (0)	7 (5.3)
Bacteremia	1 (2.2)	0 (0)	1 (0.8)
Sepsis syndrome	9 (19.6)	0 (0)	9 (6.9)

Abbreviations: cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; eGFR=estimated glomerular filtration rate; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; N=number of participants; n/a=not applicable
Source: Applicant's population PK report 08pwp8. Table 9 in page 51 and 52.

Table 35. Dosing Regimens in Studies P020 and P021

Study	Cohort	Age Range	N	Initial Dose	Modified Dose
P020	1	12 to < 18 years	7	15/7.5 mg/kg (30 min)	500/250 mg (30 mg)
	2	6 to < 12 years	6		15/7.5 mg/kg (60 min)
	3	2 to < 6 years	6		
	4	3 months to < 1 years	8	10/5 mg/kg (60 min)	
	5	Birth to < 3 months	19		
Study P021	1	12 to < 18 years	10	500 / 250 mg (30 min) q6h	500 / 250 mg (60 min) q6h
	2	6 to < 12 years	31	15/7.5 mg/kg (60 min) q6h	15/7.5 mg/kg (60 min) q6h
	3	2 to < 6 years	22		
	4	3 months to < 1 years	15		
	5	Birth to < 3 months	8	15/7.5 mg/kg (60 min) q8h	15/7.5 mg/kg (60 min) q8h

Source: Applicant's Studies P020 and P021 Study Reports.

Applicant's Population PK Model for Imipenem

The base model proposed for imipenem by the Applicant was a 2-compartment model with first elimination developed based on established model in adults. Standard allometric scaling of body weight was applied to CL and Q using a fixed exponent of 0.75, and to Vc and Vp using a fixed exponent of 1. Renal maturation as a function of PMA (RMF, where PMA is the addition of postnatal age and GA in weeks) was implemented on drug CL. The RMF was implemented on CL with fixed values of 3.4 and 47.7 for the Hill coefficient and TM50 estimates, respectively. NONMEM with FOCEI method was used for population PK model development.

Equations used were as follows:

$$CL\ (L/h)[\geq 2\ years\ old] = 15 \times \left(\frac{PMA^{3.4}}{PMA^{3.4} + 47.7^{3.4}}\right) \times \left(\frac{WT}{75}\right)^{0.75} \times \left(\frac{eGFR}{144}\right)^{0.477} \times \exp\left(eta_1\right)$$

$$CL\ (L/h)[< 2\ years\ old] = 15 \times \left(\frac{PMA^{3.4}}{PMA^{3.4} + 47.7^{3.4}}\right) \times \left(\frac{WT}{75}\right)^{0.75} \times \exp\left(eta_1\right)$$

$$Vc\ (L) = 21.2 \times \left(\frac{WT}{75}\right)^{1} \times \exp\left(eta_2\right)$$

$$Vp\ (L) = 5.55$$

$$Q\ (L/h) = 3.84$$

The final population PK model incorporates the covariate effects of body weight as allometric scaling to CL, Q, Vc and Vp, renal maturation and fixed eGFR for pediatric patients as described above. No additional covariates were identified significant in the pediatric population PK model.

The parameter estimates for the final covariate model are listed in **Table 36**. All parameters were estimated with good precision, with relative standard errors (RSEs) below 30%, except for Q (36%), and larger CIs for the IIV on Vc based on the bootstrap analysis. η shrinkage was low on CL, though above 30% (38%) for Vc. The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 5**. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in **Figure 6**.

Table 36. Parameter Estimates (RSE) and Median (95% CI) for the Applicant's Final Pediatric Imipenem Model

Parameter	Estimate	RSE%	Bootstrap Median	Bootstrap 95% CI	Shrinkage
Typical Values					
CL (L/h)	15.0	3.38	14.8	13.5 to 15.9	
Vc (L)	21.2	6.62	20.7	15.7 to 24.1	
Vp (L)	5.55	12.4	6.09	4.52 to 21.2	
Q (L/h)	3.84	36.0	3.69	2.02 to 11.5	
AS on CL and Q	0.750 Fixed	n/a	n/a	n/a	
AS on Vc and Vp	1.00 Fixed	n/a	n/a	n/a	
Renal maturation function Hill coefficient	3.40 Fixed	n/a	n/a	n/a	
Renal maturation function TM_{50} estimate	47.7 Fixed	n/a	n/a	n/a	
Renal function (eGFR-bedside Schwartz)	0.447 Fixed	n/a	n/a	n/a	
IIV (CV%)					
On CL	31.6	8.59	31.0	23.7 to 38.9	11.1%
On Vc	31.0	20.4	29.7	1.61 to 50.6	37.9%
Residual Error (CV%)					
Proportional residual error dense PK	16.2	13.3	16.0	11.0 to 22.4	29.6%
Proportional residual error sparse PK	50.9	7.85	51.2	42.3 to 62.3	11.4%

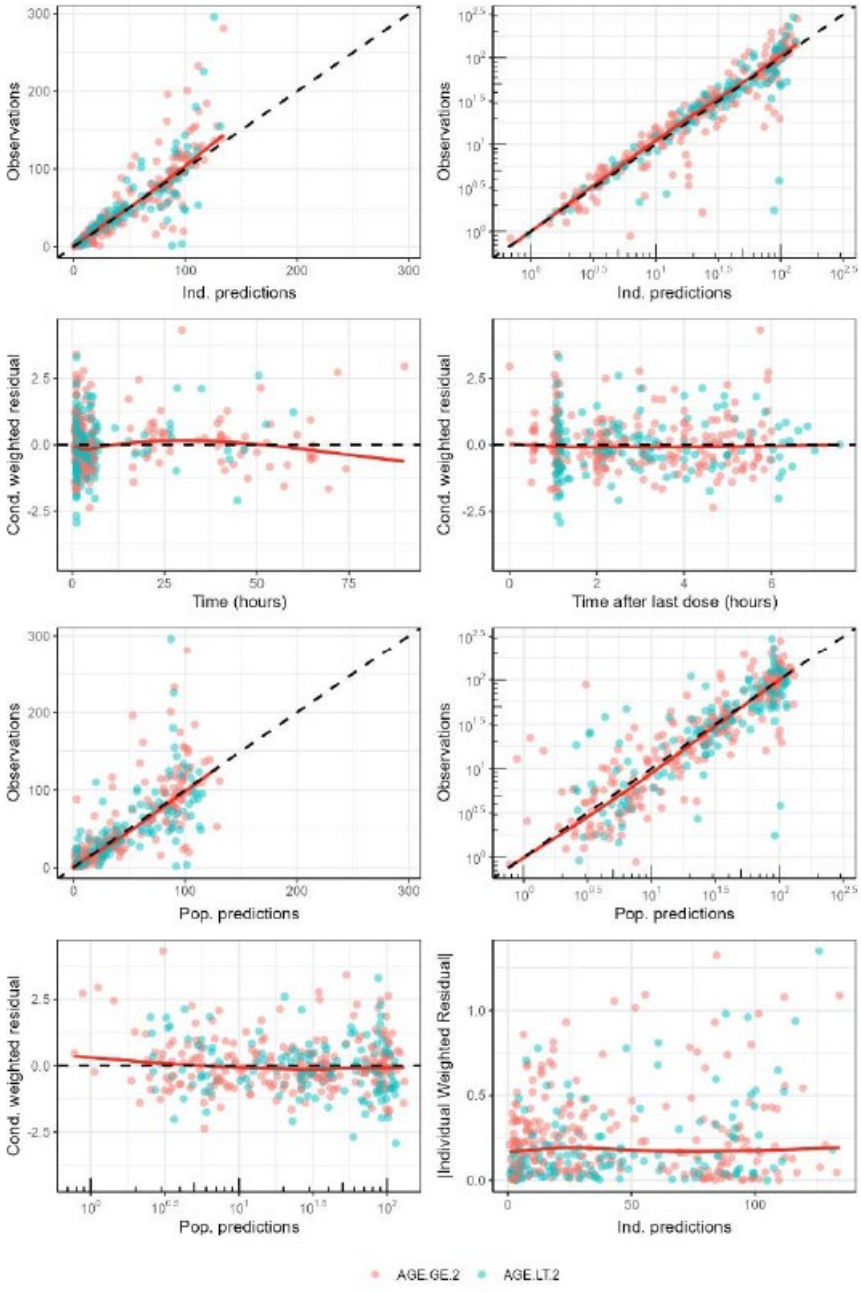
RSE% is derived from the following equation: (standard error/mean) × 100; CV% is derived from the following equation: 100 × sqrt(exp(x) - 1); bootstrap is based on n=1000 dataset replicates.

Abbreviations: AS=allometric scaling; CI=confidence interval; CL=clearance; CV=coefficient of variation; eGFR=estimated glomerular filtration rate; IIV=interindividual variability; n/a=not applicable; PK=pharmacokinetic; PMA=postmenstrual age; Q=intercompartmental clearance; RSE=relative standard

error; sqrt=square root; TM50=maturation half time; Vc=central volume of distribution; Vp=peripheral volume of distribution; WT=baseline body weight.

Source: Applicant's population PK report 08pwp8, Table 12, page 57.

Figure 5. Log-Log and Linear Standard Goodness-of-fit Plots for the Applicant's Pediatric Imipenem Model by Age Categories

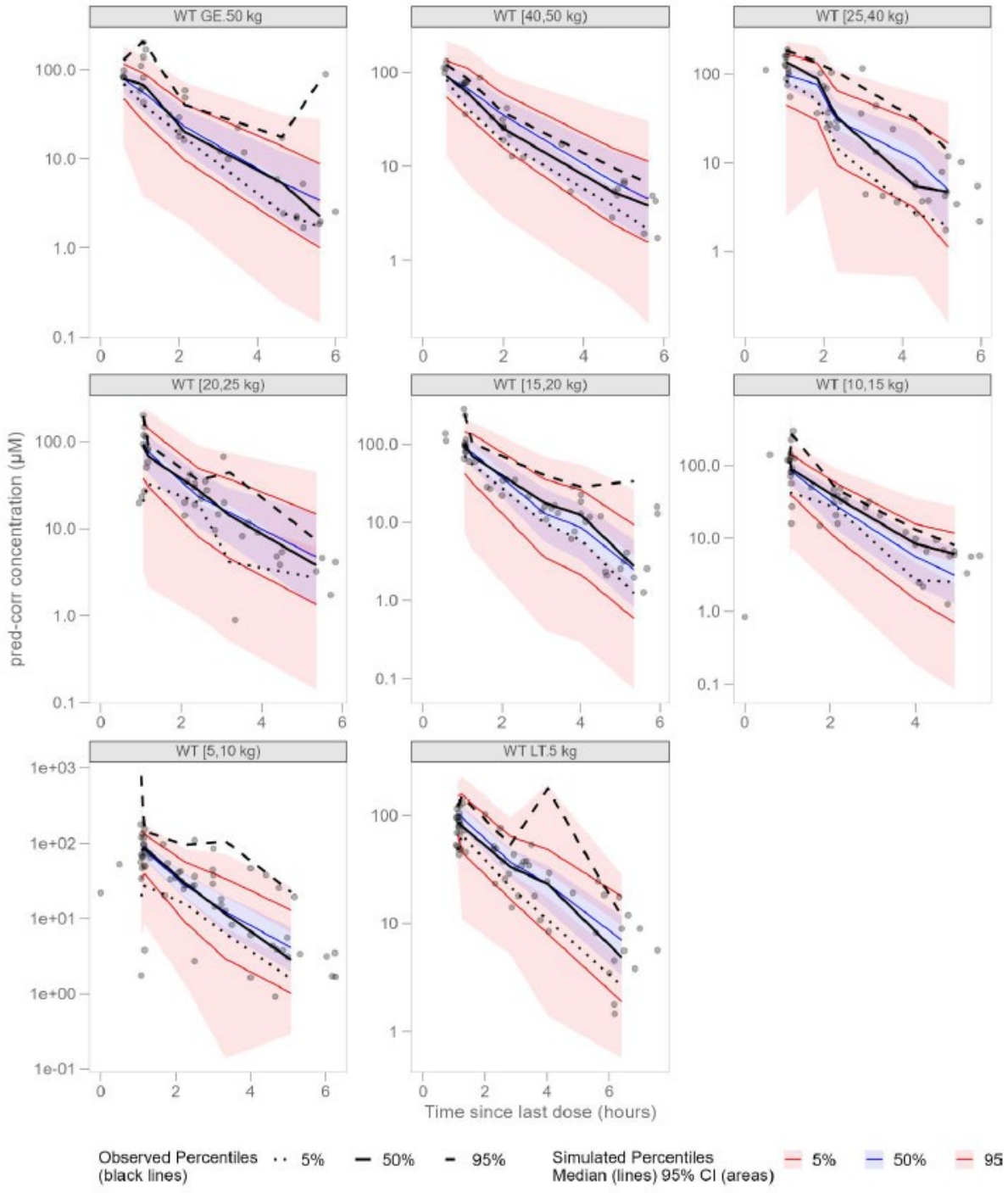


Circles represent individual observations; the red solid line represent a loess fit.

Abbreviations: AGE.GE.2=age ≥2; AGE.LT.2=age <2; CWRES=conditional weighted residuals; Ind=individual; IWRES=individual weighted residuals; loess=locally estimated scatterplot smoothing; pop=population.

Source: Applicant's population PK report 08pwp8, Figure 5, page 60.

Figure 6. pcVPC of the Applicant's final Pediatric Imipenem PopPK Model Stratified by Weight Categories



Notes: Gray circles represent individual pred-corr observations.

Abbreviations: CI=confidence interval; WT GE.50=baseline body weight ≥50; WT LT.5=baseline body weight<5; pcVPC=prediction-corrected visual predictive check; pred-corr=prediction-corrected; WT=baseline body weight.

Source: Applicant's population PK report 08pwp8, Figure 7, page 62.

Reviewer's comments:

The Applicant's pediatric population PK model for imipenem has been verified using goodness of fit and visual predictive check plots. Goodness-of-fit plots (Figure 5) demonstrate that the population PK model provides good estimations for plasma imipenem concentrations, as evidenced by consistency between individual estimated concentrations and observed values. The visual predictive checks (Figure 6) show agreement between the observed and predicted medians and 90% CI percentiles for imipenem in pediatric patients over time. As a result, the reviewer concluded that the model is acceptable for describing imipenem concentrations and covariate effects on imipenem exposure.

Applicant's Population PK Model for REL

The base model proposed for REL by the Applicant was a 2-compartment model with first elimination developed based on established model in adults. Standard allometric scaling of body weight was applied to CL and Q using a fixed exponent of 0.75, and to Vc and Vp using a fixed exponent of 1. Renal maturation as a function of PMA (RMF, where PMA is the addition of postnatal age and GA in weeks) was implemented on drug CL. The RMF was implemented on CL with fixed values of 3.4 and 47.7 for the Hill coefficient and TM50 estimates, respectively. NONMEM with FOCEI method was used for population PK model development.

Equations used were as follows:

$$CL\ (L/h)[\geq 2\ years\ old] = 9.48 \times \left(\frac{PMA^{3.4}}{PMA^{3.4} + 47.7^{3.4}}\right) \times \left(\frac{WT}{75}\right)^{0.75} \times \left(\frac{eGFR}{114}\right)^{0.65} \times \exp\left(eta_1\right)$$

$$CL\ (L/h)[< 2\ years\ old] = 9.48 \times \left(\frac{PMA^{3.4}}{PMA^{3.4} + 47.7^{3.4}}\right) \times \left(\frac{WT}{75}\right)^{0.75} \times \exp\left(eta_1\right)$$

$$Vc\ (L) = 18.4 \times \left(\frac{WT}{75}\right)^{1} \times \exp\left(eta_2\right)$$

$$Vp\ (L) = 7.72$$

$$Q\ (L/h) = 5.64$$

The final population PK model incorporates the covariate effects of body weight as allometric scaling to CL, Q, Vc and Vp, renal maturation and fixed eGFR for pediatric patients as described above. No additional covariates were identified significant in the pediatric population PK model.

The parameter estimates for the final covariate model are listed in **Table 37**. All parameters were estimated with good precision, with relative standard errors (RSEs) below 30%, except for Q (39.2%), and larger CIs for the IIV on Vc based on the bootstrap analysis. η shrinkage was low on CL, though above 30%

(38%) for Vc. The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 7**. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in **Figure 8**.

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

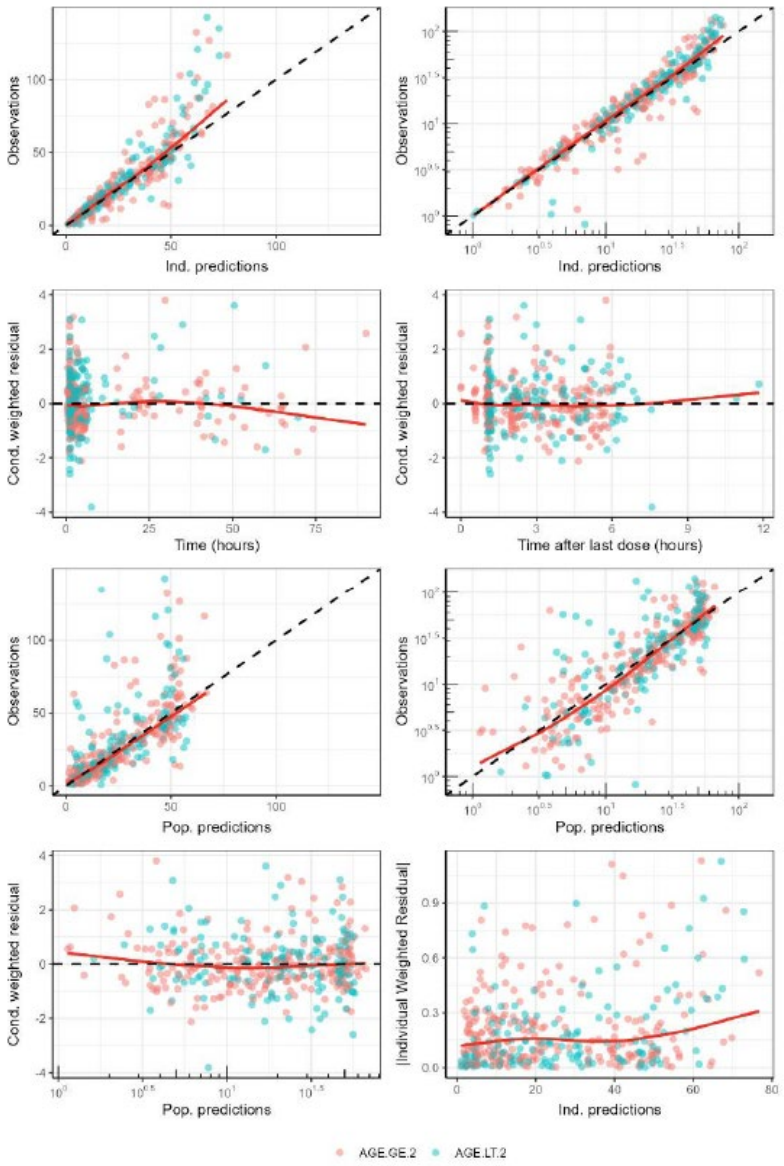
Parameter	Estimate	RSE%	Bootstrap Median	Bootstrap 95% CI	Shrinkage
Typical Values					
CL (L/h)	9.48	4.07	9.40	8.50 to 10.2	
Vc (L)	18.4	8.94	18.2	5.91 to 21.2	
Vp (L)	7.72	11.9	8.07	6.28 to 15.8	
Q (L/h)	5.64	39.2	5.22	2.99 to 21.1	
AS on CL and Q	0.750 Fixed	n/a	n/a	n/a	
AS on Vc and Vp	1.00 Fixed	n/a	n/a	n/a	
Renal maturation function Hill coefficient	3.40 Fixed	n/a	n/a	n/a	
Renal maturation function TM_{50} estimate	47.7 Fixed	n/a	n/a	n/a	
Renal function (eGFR-bedside Schwartz)	0.65 Fixed	n/a	n/a	n/a	
IIV (CV%)					
On CL	42.4	6.70	43.0	31.9 to 55.9	6.60%
On Vc	33.5	18.6	34.5	0.326 to 74.3	38.3%
Residual Error (CV%)					
Proportional residual error dense PK	16.3	11.0	15.6	9.89 to 23.5	29.2%
Proportional residual error sparse PK	44.6	7.68	43.8	35.0 to 58.1	13.5%

RSE% is derived from the following equation: (standard error/mean) × 100; CV% is derived from the following equation: 100 × sqrt(exp(x) - 1); bootstrap is based on n=1000 dataset replicates.

Abbreviations: AS=allometric scaling; CI=confidence interval; CL=clearance; CV=coefficient of variation; eGFR=estimated glomerular filtration rate; IIV=interindividual variability; n/a=not applicable; PK=pharmacokinetic; PMA=postmenstrual age; Q=intercompartmental clearance; RSE=relative standard error; sqrt=square root; TM50=maturation half time; Vc=central volume of distribution; Vp=peripheral volume of distribution; WT=baseline body weight.

Source: Applicant's population PK report 08pwp8, Table 14, page 66.

Figure 7. Log-Log and Linear Standard Goodness-of-fit Plots for the Applicant's Pediatric REL Model by Age Categories

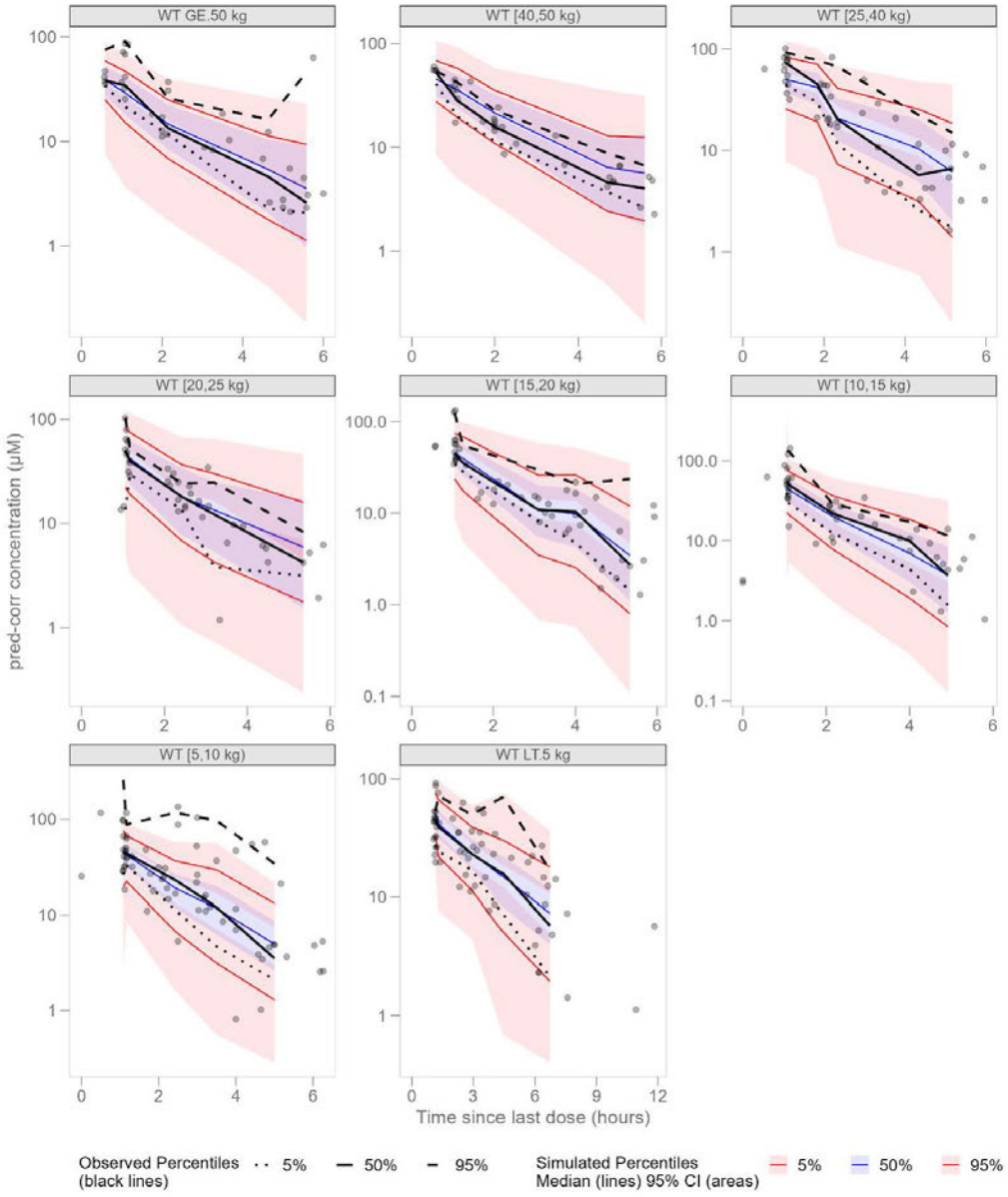


Circles represent individual observations; the red solid line represent a loess fit.

Abbreviations: AGE.GE.2=age ≥2; AGE.LT.2=age <2; CWRES=conditional weighted residuals; Ind=individual; IWRES=individual weighted residuals; loess=locally estimated scatterplot smoothing; pop=population.

Source: Applicant's population PK report 08pwp8, Figure 9, page 69.

Figure 8. pcVPC of the Applicant's final Pediatric REL PopPK Model Stratified by Weight Categories



Notes: Gray circles represent individual pred-corr observations.

Abbreviations: CI=confidence interval; WT GE.50=baseline body weight ≥50; WT LT.5=baseline body weight<5; pcVPC=prediction-corrected visual predictive check; pred-corr=prediction-corrected; WT=baseline body weight; REL=relebactam.

Source: Applicant's population PK report 08pwp8, Figure 11, page 71.

Reviewer's comments:

The Applicant's pediatric population PK model for REL has been verified using goodness of fit and visual predictive check plots. Goodness-of-fit plots (Figure 5) demonstrate that the population PK model provides good estimations for plasma REL concentrations, as evidenced by consistency between individual

estimated concentrations and observed values. The visual predictive checks (Figure 6) show agreement between the observed and predicted medians and 90% CI percentiles for REL in pediatric patients over time. As a result, the reviewer concluded that the model is acceptable for describing REL concentrations and covariate effects on REL exposure.

15.3.1.4. Simulations

- **Patients with normal renal function**

The final pediatric PPK models for imipenem and REL, respectively, were used to perform all simulations for cIAI/cUTI pediatric patients. In addition, as the covariate effects of pneumonia on the CL and Vc were not included in the pediatric models due to insufficient data, a sensitivity analysis was conducted by introducing in the pediatric models the effects of infection types (HABP/VABP versus cIAI/cUTI) using identified values. Specifically, a decrease of 38% and 39% was assumed, respectively, on CL and Vc for imipenem, and a decrease of 43% and 29% was assumed, respectively, on CL and Vc for REL.
The virtual pediatric population consisted of 10000 patients per infection type (N=2000 per age cohort) with a median [range] body weight of 16.7 kg [2.38, 154], age of 3.0 years [0.000139, 17.0], and eGFR based on bedside Schwartz of 129 mL/min/1.73 m2 [90.0, 232] (only in pediatric patients of 2 years of age and older).

Simulations were conducted to determine a potential dosing regimen in pediatric cIAI/cUTI and HABP/VABP patients that could produce comparable exposures in an adult patient with the same infections (Table 38).

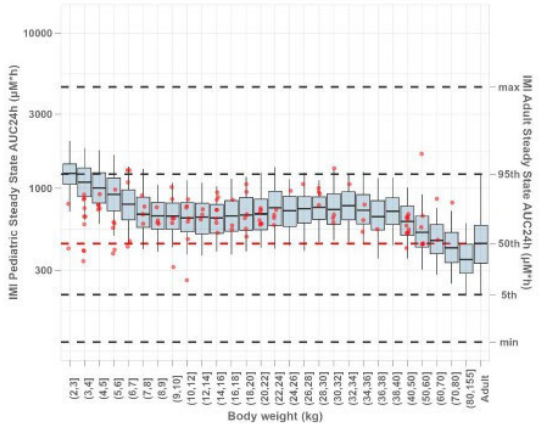
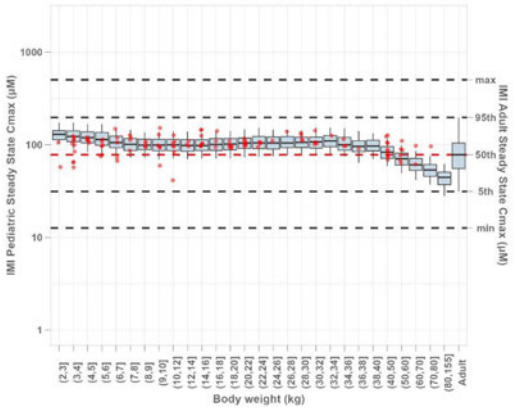
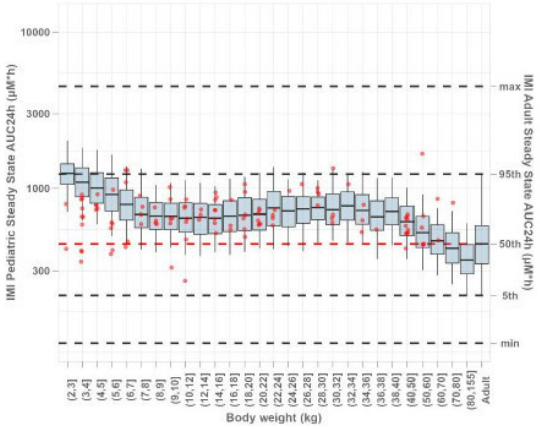
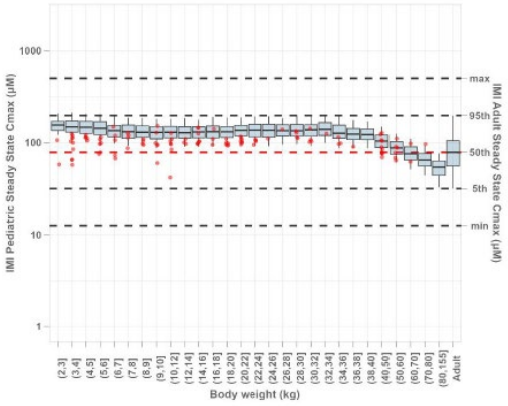
Table 38. Summary of Stimulation Scenarios for Normal Renal Function and Renal Impairment Categories.

Model	Infection Type	Scenario Number	Renal Function	N	Demographics	Dosage	Dosing Frequency	Infusion Duration (minutes)
Final	cIAI/cUTI	1	Normal eGFR ≥90 mL/min/1.73 m²	10000	Age: Birth to <1 year Weight: 2.38 to 154 kg	Actual Study P021	See MAP, [Sec. 9.1], Table 3	
		2				15/7.5 mg/kg	q6h	30
		3						60
		4					q8h	30
		5						60
		6					q12h	30
		7						60
		8				Recommended	See Table 32	
		9	Mild RI eGFR [60 to <90) mL/min/1.73 m²	3155	Age: <18 years Weight: ≥30 kg	400/200 mg	q6h	30
		10		2845	Age: ≥2 years Weight: <30 kg	12/6 mg/kg		60
		11	Moderate RI eGFR [30 to <60) mL/min/1.73 m²	3155	Age: <18 years Weight: ≥30 kg	300/150 mg		30
		12		2845	Age: ≥2 years Weight: <30 kg	9/4.5 mg/kg		60
		13	Severe RI eGFR [15 to <30) mL/min/1.73 m²	3155	Age: <18 years Weight: ≥30 kg	200/100 mg		30
		14		2845	Age: ≥2 years Weight: <30 kg	6/3 mg/kg		60
		15	ESRD eGFR [4 to <15) mL/min/1.73 m²	3155	Age: <18 years Weight: ≥30 kg	200/100 mg		30
		16		2845	Age: ≥2 years Weight: <30 kg	6/3 mg/kg		60

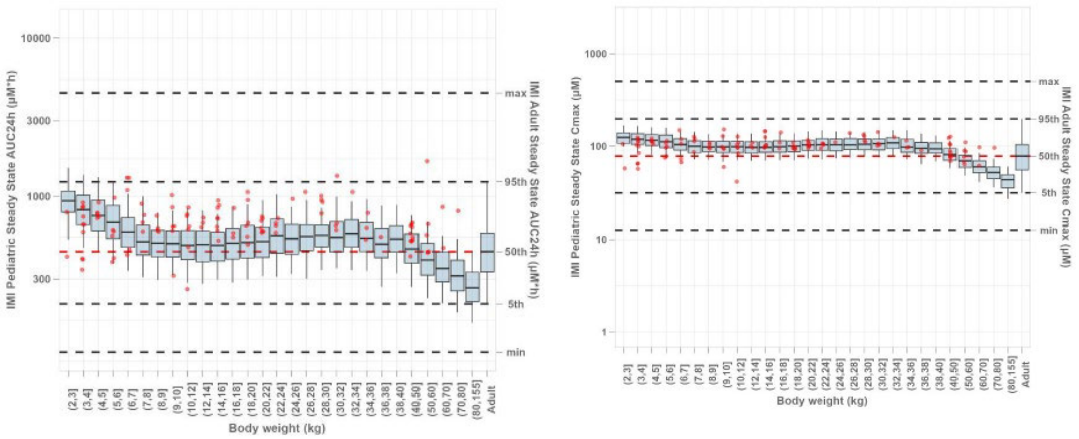
Source: Applicant's population PK report 08pwp8, Table 31, pages 113.

Resuluts (Figure 9) indicated that patients weighing ≥30 kg receiving a q6h regimen with a 30-minute infusion duration are expected to have both imipenem steady-state AUC0-24h and Cmax exposures well within the adult clinical PK experience. For patients < 30 kg, virtual patients receiving the same 30-minute infusion are expected to have an increase in C_{max} as compared to the upper reference threshold of adult experience (Figure 9). Extending the infusion to a 60-minute duration allows pediatric patients <30 kg to maintain C_{max} values closer to the median adult experience and well within the adult 95th percentile. In virtual pediatric patients' birth to <3 months of age (corresponding to patients < 8 kg), the q6h dosing frequency results in $AUC_{0\text{-}24h}$ exceeding the 95th percentile of adult experience in a large proportion of patients (Figure 9). A q8h dosing frequency as compared to q6h dosing frequency with 60-minute infusion duration was found to result in less excursions in C_{max} while maintaining similar $AUC_{0\text{-}24h}$ to the adult population (Figure 9). Similar interpretations and conclusions were true for REL (Figure 10).

Figure 9. Distribution of Model-simulated Imipenem Steady-State $AUC_{0\text{-}24h}$ (Top) and C_{max} (Bottom) in cIAI/cUTI by Weight Bins Following Multiple IV Administrations in Virtual Pediatric Patients.

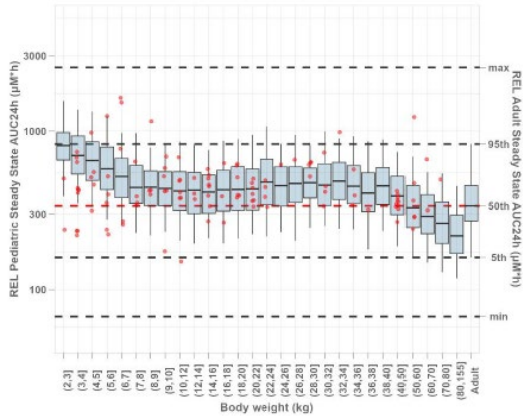
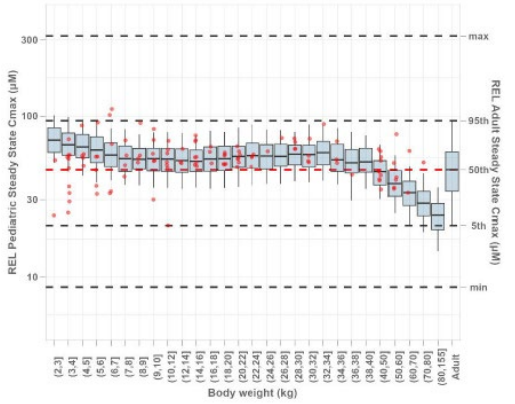
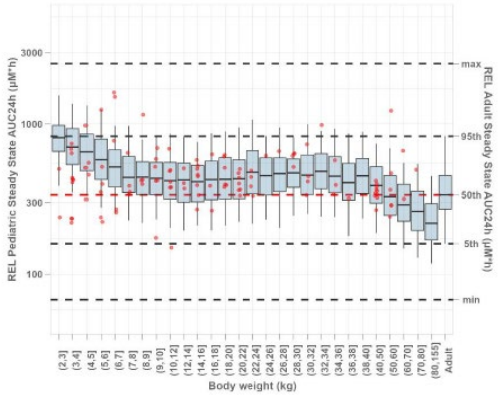
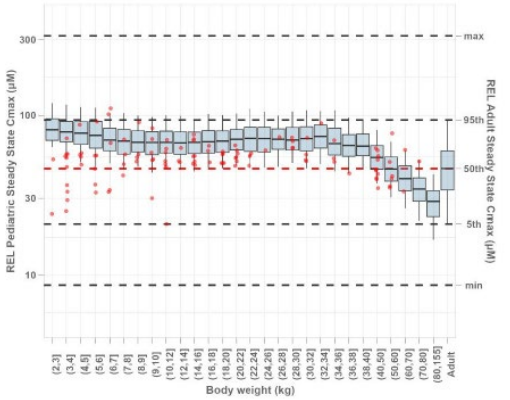
Dosing Regimen	AUC0-24h	Cmax
15/7.5 mg/kg IMI/REL q6h with an Infusion Duration of 60 Min		
15/7.5 mg/kg IMI/REL q6h with an Infusion Duration of 30 Min		

15/7.5 mg/kg IMI/REL q8h with an Infusion Duration of 60 Min

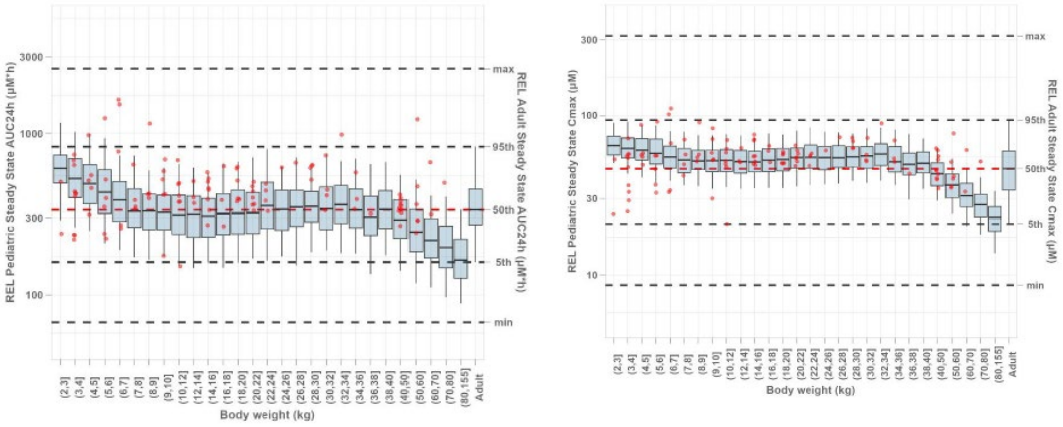


IMI=imipenem
Source: Applicant's population PK report 08pwp8, Figures 114 - 116, pages 345-350.

Figure 10. Distribution of Model-simulated REL Steady-State $AUC_{0\text{-}24h}$ (Top) and C_{max} (Bottom) in cIAI/cUTI by Weight Bins Following Multiple IV Administrations in Virtual Pediatric Patients.

Dosing Regimen	AUC0-24h	Cmax
15/7.5 mg/kg IMI/REL q6h with an Infusion Duration of 60 Min		
15/7.5 mg/kg IMI/REL q6h with an Infusion Duration of 30 Min		

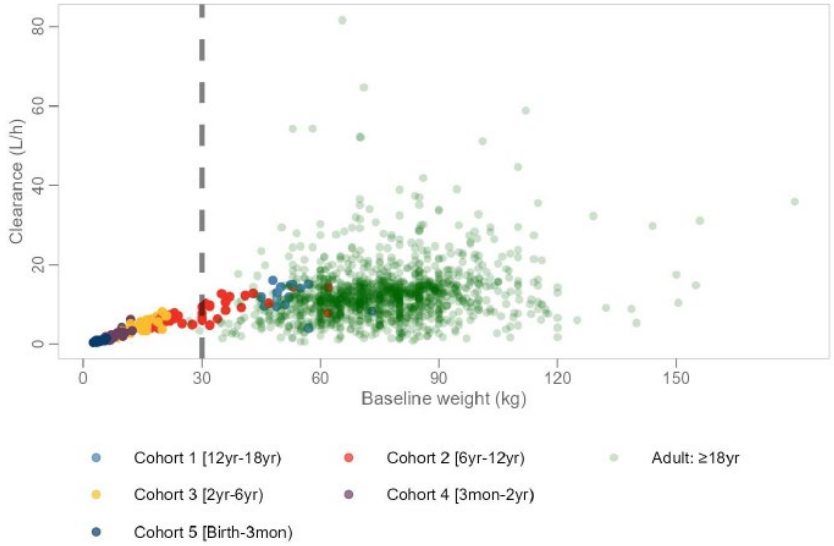
15/7.5 mg/kg IMI/REL q8h with an Infusion Duration of 60 Min



IMI=imipenem
Source: Applicant's population PK report 08pwp8, Figures 118 - 120, pages 353-358.

As shown in Figure 11, imipenem clearance increased with body weight until approximately 30 kg and reached a plateau afterwards, providing supporting evidence for selecting 30 kg as the cut-off. As a result, 30 kg was selected as the cut-off for the weight-based dosing regimen in pediatric patients, with fixed dosing for pediatric patients ≥ 30 kg and body weight-based mg/kg dosing for those < 30 kg (**Table 39**).

Figure 11. Empirical Bayes Estimate of Relationship Between Clearance and Baseline Weight from the Final Imipenem Model (run1509) and Adult Model (run105) Colored by Age Cohort



Note: The black dashed line represents the cutoff body weight of 30 kg.
Source: Applicant's population PK report 08pwp8, Figure 77, pages 226.

Comparison of the steady-state $AUC_{0\text{-}24h}$ and C_{max} for the virtual pediatric populations (birth to <18 years) with normal renal function categorized by the proposed dose groups (**Table 39**) are presented in **Figure 12** and **Figure 13**. The post hoc exposures from Studies P020 and P021 participants receiving the protocol-based regimen are overlayed in the same figures. These pediatric data were compared to adult reference exposures that are presented both as boxplots as well as horizontal reference lines.

Table 39. Proposed IMI/REL Dosing Regimen Recommendations in Pediatric Patients (Birth to <18 Years of Age) With Normal Renal Function.

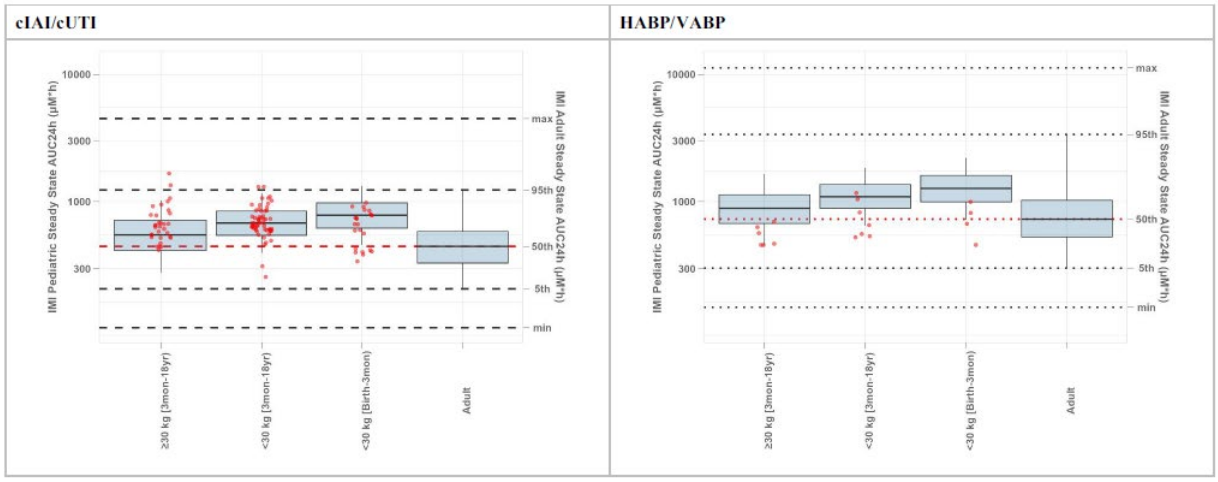
Type of Infection	Body Weight	Age	Dose (IMI and REL)[b]	Dosing Frequency	Infusion Duration
cIAI or cUTI or HABP/VABP	≥30 kg	<18 years	1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg)	q6h	30 minutes
	<30 kg	≥3 months to <18 years	37.5 mg/kg (imipenem 15 mg/kg, cilastatin 15 mg/kg, and relebactam 7.5 mg/kg)	q6h	60 minutes
		Birth to <3 months[c]	37.5 mg/kg (imipenem 15 mg/kg, cilastatin 15 mg/kg, and relebactam 7.5 mg/kg)	q8h	60 minutes

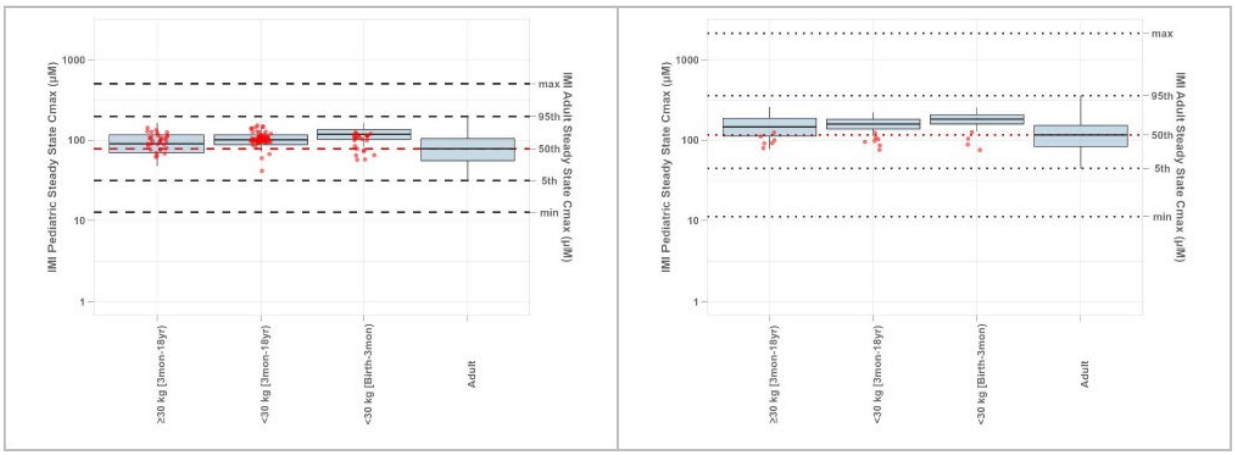
a. IMI/REL is a combination product in a fixed 2:1 ratio. Dosage recommendations are based on the imipenem and REL components.
b. IMI/REL is not recommended for preterm pediatric patients and patients weighing <2 kg.

Abbreviations: cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI=imipenem/cilastatin; IMI/REL=imipenem/cilastatin/relebactam combination; q6h=every 6 hours; q8h=every 8 hours; REL=relebactam.

Source: Applicant's population PK report 08pwp8, Table 32, pages 117.

Figure 12. Comparison of Imipenem Final Pediatric PPK Model-Predicted Steady-State Exposures (AUC0-24h [Top] and Cmax [Bottom]) Between Virtual Pediatric Population Following Administration of Recommended IMI/REL Dosing Regimen and Studied Pediatric Patients and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI/REL Dosing Regimen Administration

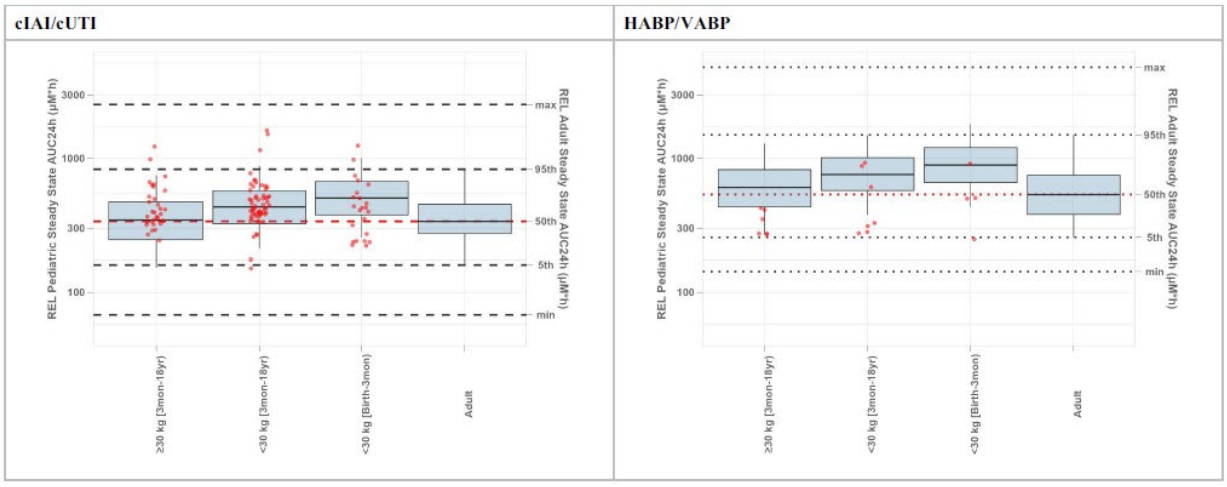


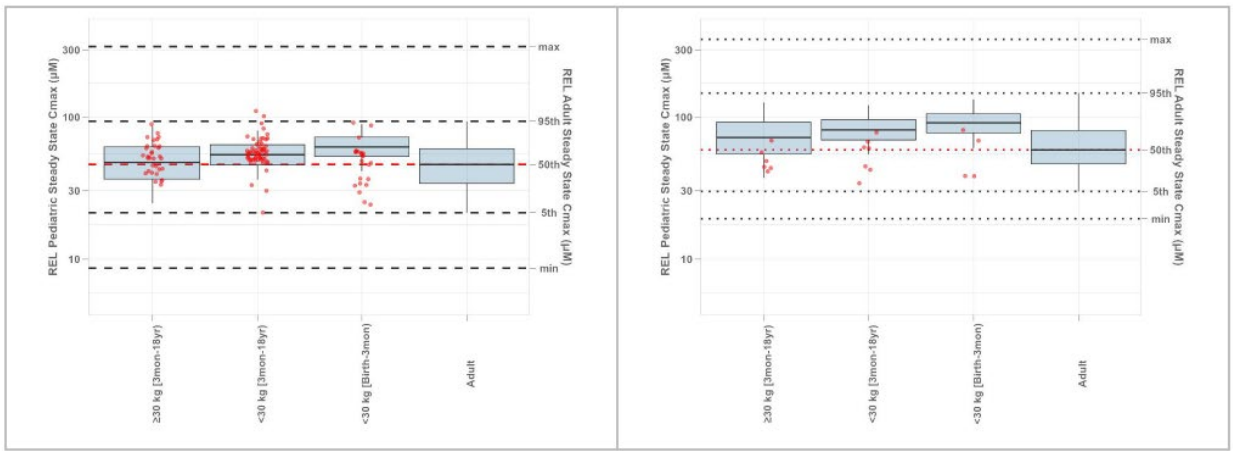


Boxplots represent the simulated pediatric exposures similated from the proposed dosing regimen; the blue area represents the interquartile interval; the thick black line corresponds to the median; and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Red circles represent individual post hoc exposures in pediatric patients from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type. Adult exposures are the PPK-predicted exposures from Phase 2/3 studies. Red circles represent individual post hoc exposures in pediatric patients from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type.

Source: Applicant's population PK report 08pwp8, Table 28, pages 118-119.

Figure 13. Comparison of REL Final Pediatric PPK Model-Predicted Steady-State Exposures (AUC0-24h [Top] and Cmax [Bottom]) Between Virtual Pediatric Population Following Administration of Recommended IMI/REL Dosing Regimen and Studied Pediatric Patients and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI/REL Dosing Regimen Administration





Boxplots represent the simulated pediatric exposures similated from the proposed dosing regimen; the blue area represents the interquartile interval; the thick black line corresponds to the median; and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Red circles represent individual post hoc exposures in pediatric patients from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type. Adult exposures are the PPK-predicted exposures from Phase 2/3 studies. Red circles represent individual post hoc exposures in pediatric patients from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type.

Source: Applicant's population PK report 08pwp8, Table 29, pages 120-121.

Exposures parameters were derived for the virtual pediatric population at the recommended dosing regimne (**Table 39)** for imipenem (**Table 40**) and REL (**Table 41)**, respectively.

Table 40. Pediatric PPK Model-Predicted Steady-State PK Parameter Values for Imipenem Following Multiple IMI/REL Recommended Dosing Regimen Administration in the Virtual Pediatric Population

Age	Weight	IMI/REL Dose (infusion Duration, Minutes)	Descriptive Statistic	Key PK Parameters for Imipenem						
				$AUC_{0\text{-}24h}$ (μM.hr)	Cmax (μM)	$t_{1/2}$ (hr)	CL (L/hr)	CL/WT (L/hr/kg)	Vc (L)	Vc/WT (L/kg)
≥30 kg	<18 years	500/250 mg q6h (30 minutes)	N	6310	6310	6310	6310	6310	6310	6310
			Mean (SD)	787 (378)	126 (55.3)	1.87 (0.46)	10.6 (5.23)	0.194 (0.082)	13.3 (7.32)	0.237 (0.0944)
			GM (%GCV)	707 (48.1)	115 (44)	1.82 (24.7)	9.45 (49.6)	0.178 (42.4)	11.7 (5)	0.22 (39.8)
			Median [Min, Max]	714 [136, 3400]	115 [22.9, 383]	1.79 [1.02, 5.22]	9.36 [1.97, 49]	0.178 [0.0463, 0.633]	11.6 [2.64, 71.6]	0.219 [0.0593, 0.732]
			5th to 95th	321 to 1510	54.8 to 232	1.3 to 2.74	4.43 to 20.8	0.0904 to 0.348	5.03 to 27.2	0.117 to 0.415
<30 kg	≥3 months and <18 years	15/7.5 mg/kg q6h (60 minutes)	N	9690	9690	9690	9690	9690	9690	9690
			Mean (SD)	944 (393)	133 (40.8)	1.4 (0.356)	3.81 (2.17)	0.25 (0.103)	3.67 (2.16)	0.238 (0.0945)
			GM (%GCV)	871 (41.6)	127 (30.7)	1.36 (25.5)	3.26 (57)	0.23 (41.4)	3.12 (58.8)	0.22 (39.8)
			Median [Min, Max]	873 [207, 4180]	127 [46.3, 342]	1.33 [0.673, 4.5]	3.36 [0.38, 17.6]	0.23 [0.0479, 0.968]	3.19 [0.419, 16.9]	0.221 [0.0625, 0.856]
			5th to 95th	447 to 1680	77.5 to 207	0.963 to 2.06	1.19 to 8	0.119 to 0.448	1.17 to 7.84	0.117 to 0.415
<30 kg	birth to <3 months	15/7.5 mg/kg q8h (60 minutes)	N	4000	4000	4000	4000	4000	4000	4000
			Mean (SD)	1090 (468)	153 (45.8)	1.61 (0.527)	0.729 (0.354)	0.164 (0.0689)	1.05 (0.48)	0.238 (0.0952)
			GM (%GCV)	997 (43.1)	146 (30)	1.54 (32.6)	0.652 (48.6)	0.151 (42)	0.954 (45.7)	0.22 (40)
			Median [Min, Max]	987 [253, 5110]	146 [47.7, 369]	1.5 [0.646, 4.86]	0.658 [0.145, 3.04]	0.152 [0.0294, 0.595]	0.956 [0.234, 3.91]	0.222 [0.0663, 0.808]
			5th to 95th	512 to 2000	89.5 to 235	0.972 to 2.63	0.296 to 1.41	0.0753 to 0.294	0.465 to 1.95	0.115 to 0.413

Source: Applicant's population PK report 08pwp8, Table 43, pages 138.

Table 41. Pediatric PPK Model-Predicted Steady-State PK Parameter Values for REL Following Multiple IMI/REL Recommended Dosing Regimen Administration in the Virtual Pediatric Population

Age	Weight	IMI/REL Dose (infusion duration, minutes)	Descriptive Statistic	Key PK Parameters for Relebactam						
				$AUC_{0\text{-}24h}$ (μM.hr)	Cmax (μM)	$t_{1/2}$ (hr)	CL (L/hr)	CL/WT (L/hr/kg)	Vc (L)	Vc/WT (L/kg)
≥30 kg	<18 years	500/250 mg q6h (30 minutes)	N	6310	6310	6310	6310	6310	6310	6310
			Mean (SD)	549 (327)	64 (27.8)	2.32 (0.862)	7.19 (4.41)	0.132 (0.0726)	12.4 (6.58)	0.221 (0.0826)
			GM (%GCV)	469 (59.6)	58.4 (43.4)	2.19 (37.2)	6.12 (61.3)	0.115 (55)	11 (53.1)	0.207 (37.4)
			Median [Min, Max]	473 [67.7, 3310]	59.1 [11, 213]	2.12 [0.97, 8.54]	6.07 [0.868, 42.4]	0.115 [0.0199, 0.606]	11 [2.21, 66.1]	0.206 [0.0558, 0.683]
			5th to 95th	180 to 1170	28.2 to 118	1.36 to 3.99	2.45 to 15.9	0.0491 to 0.272	4.89 to 24.9	0.115 to 0.376
<30 kg	≥3 months and <18 years	15/7.5 mg/kg q6h (60 minutes)	N	9690	9690	9690	9690	9690	9690	9690
			Mean (SD)	661 (356)	70.1 (22.9)	1.76 (0.681)	2.59 (1.76)	0.169 (0.0905)	3.42 (1.95)	0.222 (0.0831)
			GM (%GCV)	581 (53.8)	66.6 (32.7)	1.65 (38.7)	2.1 (68.1)	0.148 (53.6)	2.93 (57.1)	0.207 (37.5)
			Median [Min, Max]	580 [92.8, 4380]	66.5 [20.7, 251]	1.6 [0.645, 9.05]	2.15 [0.185, 16.1]	0.149 [0.0196, 0.928]	3 [0.4, 15.5]	0.207 [0.059, 0.808]
			5th to 95th	249 to 1340	39.5 to 113	1.01 to 3.01	0.686 to 6.02	0.0644 to 0.345	1.12 to 7.25	0.114 to 0.378
<30 kg	birth to <3 months	15/7.5 mg/kg q8h (60 minutes)	N	4000	4000	4000	4000	4000	4000	4000
			Mean (SD)	767 (420)	78.1 (24.6)	2.21 (1.03)	0.486 (0.285)	0.109 (0.0579)	0.979 (0.428)	0.222 (0.0839)
			GM (%GCV)	672 (54.8)	74.5 (31.5)	2.02 (46.7)	0.416 (58.7)	0.0961 (53)	0.898 (43.7)	0.207 (37.8)
			Median [Min, Max]	666 [119, 5230]	74.5 [22.2, 279]	1.96 [0.612, 10.3]	0.421 [0.0631, 2.77]	0.0969 [0.0123, 0.541]	0.896 [0.223, 3.53]	0.208 [0.0629, 0.76]
			5th to 95th	293 to 1580	45.2 to 123	1.07 to 4.22	0.164 to 1.03	0.0409 to 0.22	0.455 to 1.78	0.113 to 0.376

Source: Applicant's population PK report 08pwp8, Table 44, pages 139.

Reviewer's Comments:

The simulated pediatric exposures at the proposed dosing regimen were contained within the 5th to 95th percentiles of adult exposure for patients with cIAI/cUTI or HABP/VABP infections, suggesting that the proposed dosing regimen for pediatric patients without renal impairment is acceptable.

- **Patients with impaired renal function**

Table 42. Proposed Dosage for Adult and Pediatric Patients (Weighing at Least 30 kg) with Renal Impairment

Estimated Renal Function eGFR [mL/min/1.73 m^2]	Recommended Dosage of imipenem/cilastatin and relebactam) (mg)	Dosing Interval
60 to 89	1 gram (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	Every 6 hours
30 to 59	0.75 grams (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	Every 6 hours
15 to 29	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours
End Stage Renal Disease (ESRD) on Hemodialysisc	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours

- Administer by IV over 30 minutes.
- Administration should be timed to follow hemodialysis.

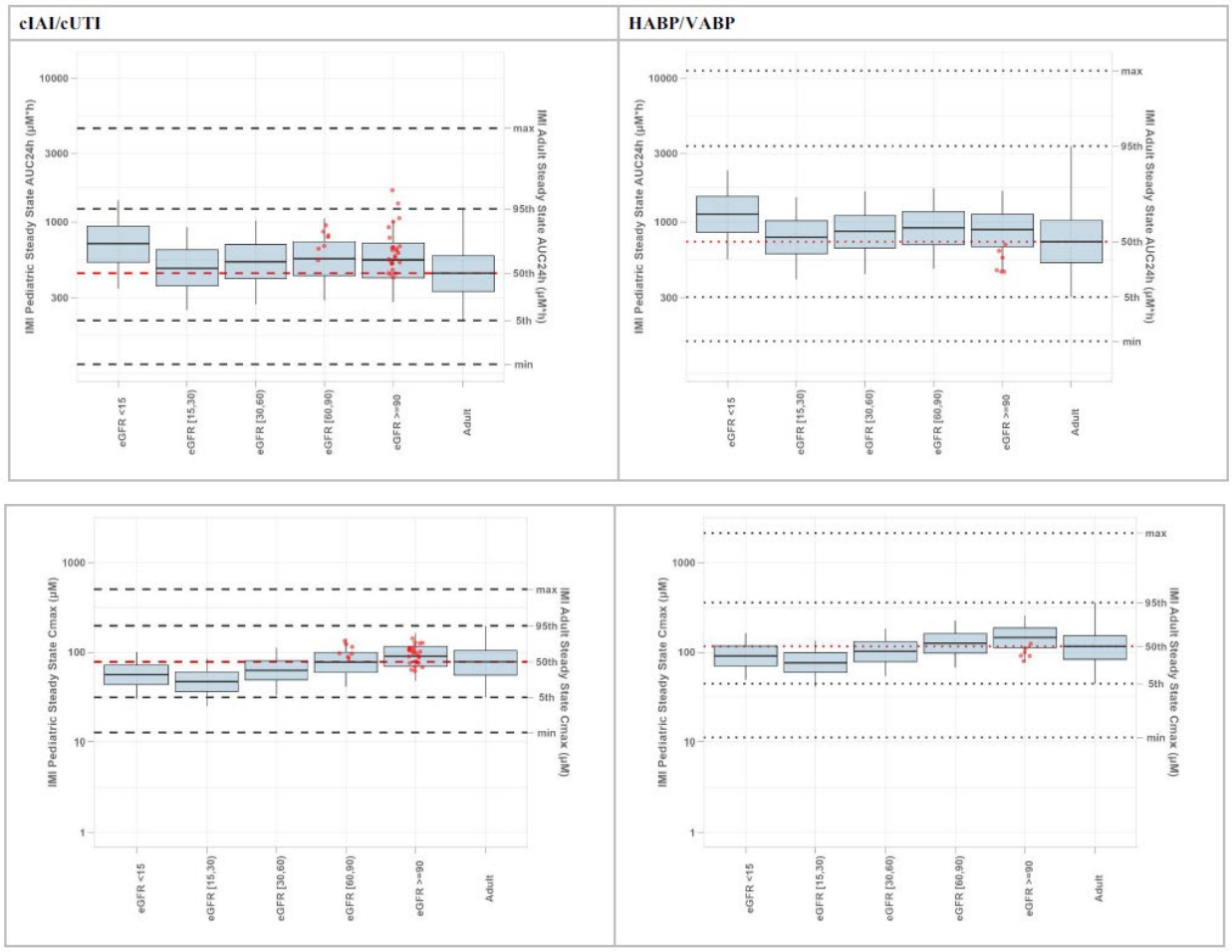
Source: applicant's proposed USPI.

Boxplots of steady-state AUC_{0-24h} and C_{max} for the virtual pediatric population ≥30 kg and <18 years stratified by renal impairment (RI) categories are presented in **Figure 14** and **Figure 15** for imipenem and REL, respectively.

The table above displays proposed dosage for adult and pediatric patients weighing at least 30 kg with renal impairment.

All simulated RI pediatric imipenem AUC_{0-24h} exposures are contained within the 5th to 95th percentiles of the adult experience with normal renal conditions except ESRD (eGFR <15 mL/min/1.73 m^2) cIAI/cUTI, where the 95th percentile of RI pediatrics slightly exceeded the 95th percentile of adults with normal renal function but still within the adult maximum exposures. Simulated RI pediatric Cmax values were generally contained within the 5th to 95th percentiles of the adult experience. The simulated RI pediatric AUC_{0-24h} and C_{max} were comparable to the corresponding exposures obtained in pediatric patients with normal renal function within the same body weight and age range.

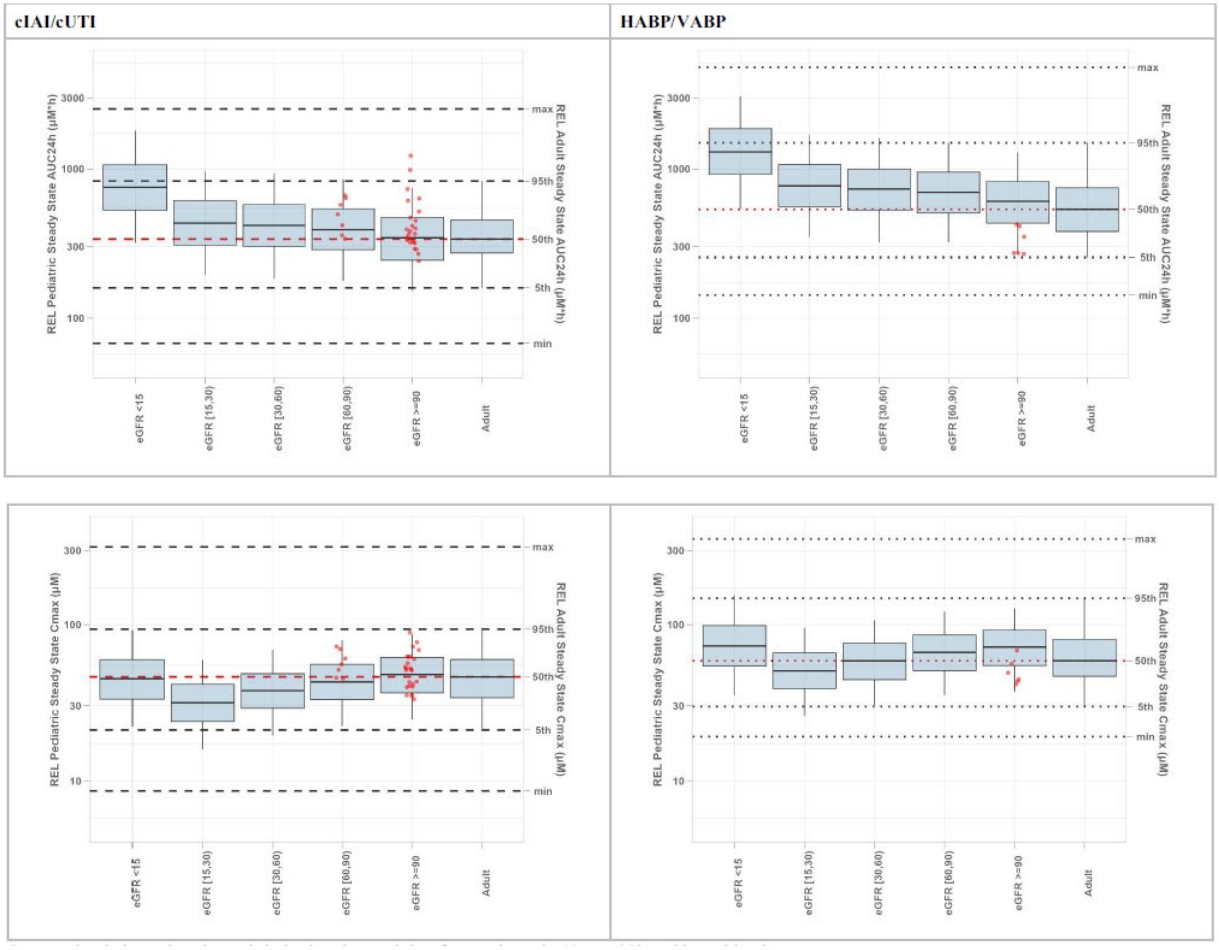
Figure 14. Comparison of Imipenem Final Pediatric PPK Model-Predicted Steady-State Exposures (AUC0-24h [Top] and Cmax [Bottom]) in Virtual Pediatric Renal Impairment Population ≥30 kg and <18 Years Following Adjusted IMI/REL Dosing Regimen Administration and in Studied Pediatric Patients with Normal Renal Function and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI/REL Dosing Regimen Administration



Adult exposures are the PPK-predicted exposures from Phase 2/3 studies. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. Red circles represent individual post hoc exposures in pediatric patients ≥30 kg from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type.

Source: Applicant's population PK report 08pwp8, Figure 38, pages 141 - 142.

Figure 15. Comparison of REL Final Pediatric PPK Model-Predicted Steady-State Exposures (AUC0-24h [Top] and Cmax [Bottom]) in Virtual Pediatric RI Population ≥30 kg and <18 Years Following Adjusted IMI/REL Dosing Regimen Administration and in Studied Pediatric Patients with Normal Renal Function and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI/REL Dosing Regimen Administration



Adult exposures are the PPK-predicted exposures from Phase 2/3 studies. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. Red circles represent individual post hoc exposures in pediatric patients ≥30 kg from Studies P020 and P021 following the protocol-based dosing regimen and stratified by infection type.

Source: Applicant's population PK report 08pwp8, Figure 39, pages 143 - 144.

Reviewer's Comments:

The simulation results for AUC0-24h and Cmax of imipenem and REL in pediatric patients (weighing ≥30 kg and <18 years of age) with mild, moderate and severe renal impairment following adjusted dosing regimen demonstrate comparable exposure to adult patients with normal renal function. However, eGFR < 15 mL/min/1.73m² demonstrate higher drug exposure for imipenem and REL compared to adult patients with normal renal function and pediatric patients with eGFR ≥ 15 mL/min/1.73m². An information request was sent to the applicant on 07/17/2025 to justify this higher exposure observed in pediatric patients with severe renal impairment (eGFR < 15 mL/min/1.73m²) at the proposed dosing regimens is clinically acceptable.

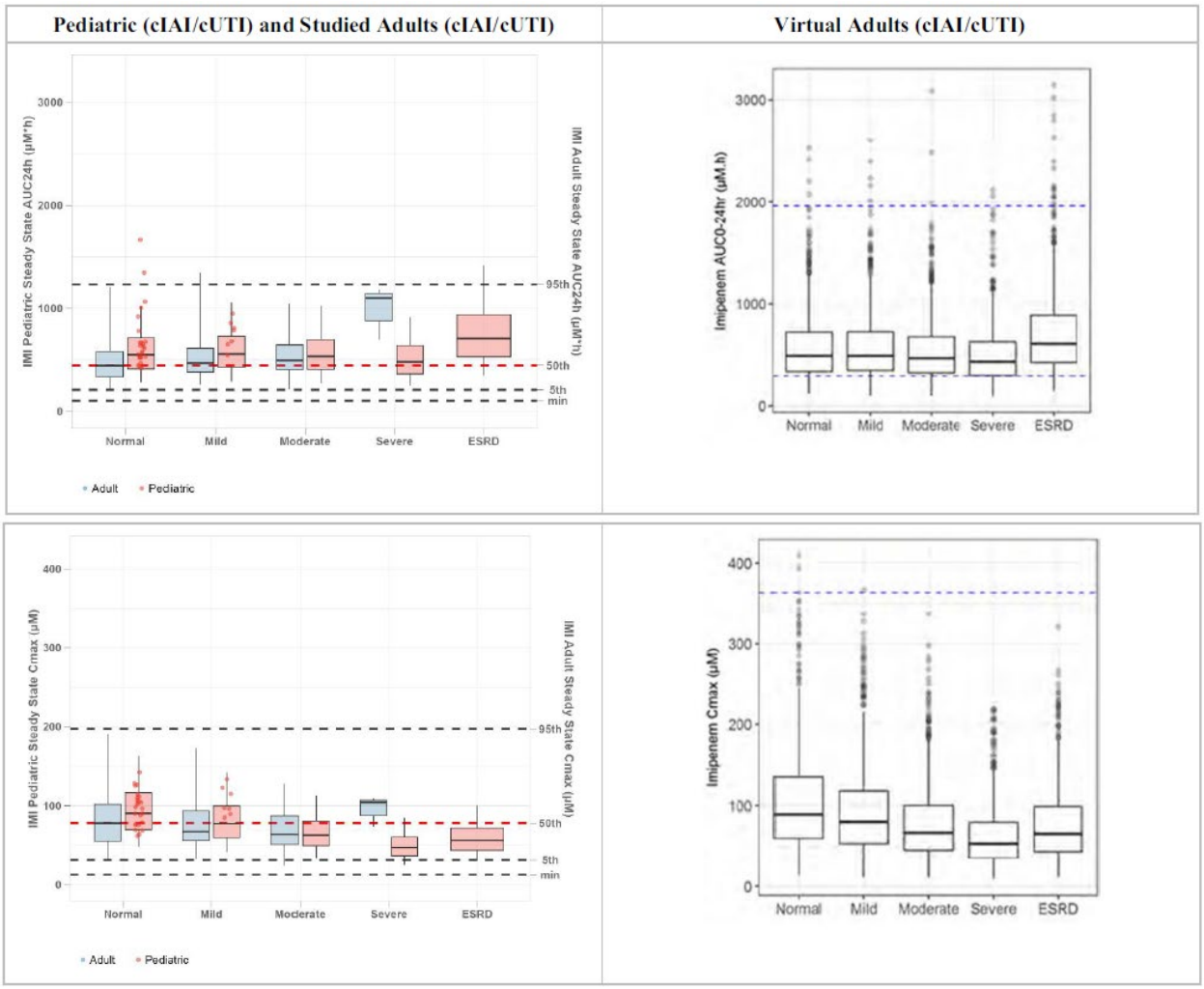
The response from the sponsor was received on 08/07/2025 (SDN 622). According to the applicant, although higher exposure was observed in pediatric patients with eGFR < 15 mL/min/1.73m², this trend is consistent with that expected and observed in adult patients with renal impairment. Both adults and

pediatrics demonstrated a trend of higher exposure in patients with ESRD (eGFR < 15 mL/min/1.73m²) compared to patients with normal renal function, with similar magnitude in adults and pediatric patients (**Table 43**, imipenem, approximately 40% for adults and 30% for pediatric patients); (**Table 44**, REL, approximately 150% for adults and 120% for pediatric patients).

Moreover, the distribution of imipenem and REL PK exposures expected in pediatric patients (≥30 kg and <18 years of age) with an eGFR < 15 mL/min/1.73m² are still expected to be within the distribution of exposures observed in adult patients with normal renal function (**Figure 16** and **Figure 17**) and for which efficacy and an acceptable safety profile have been established.

The reviewer concluded that the proposed dose adjustment in pediatric patients (≥30 kg) with renal impairment is reasonable.

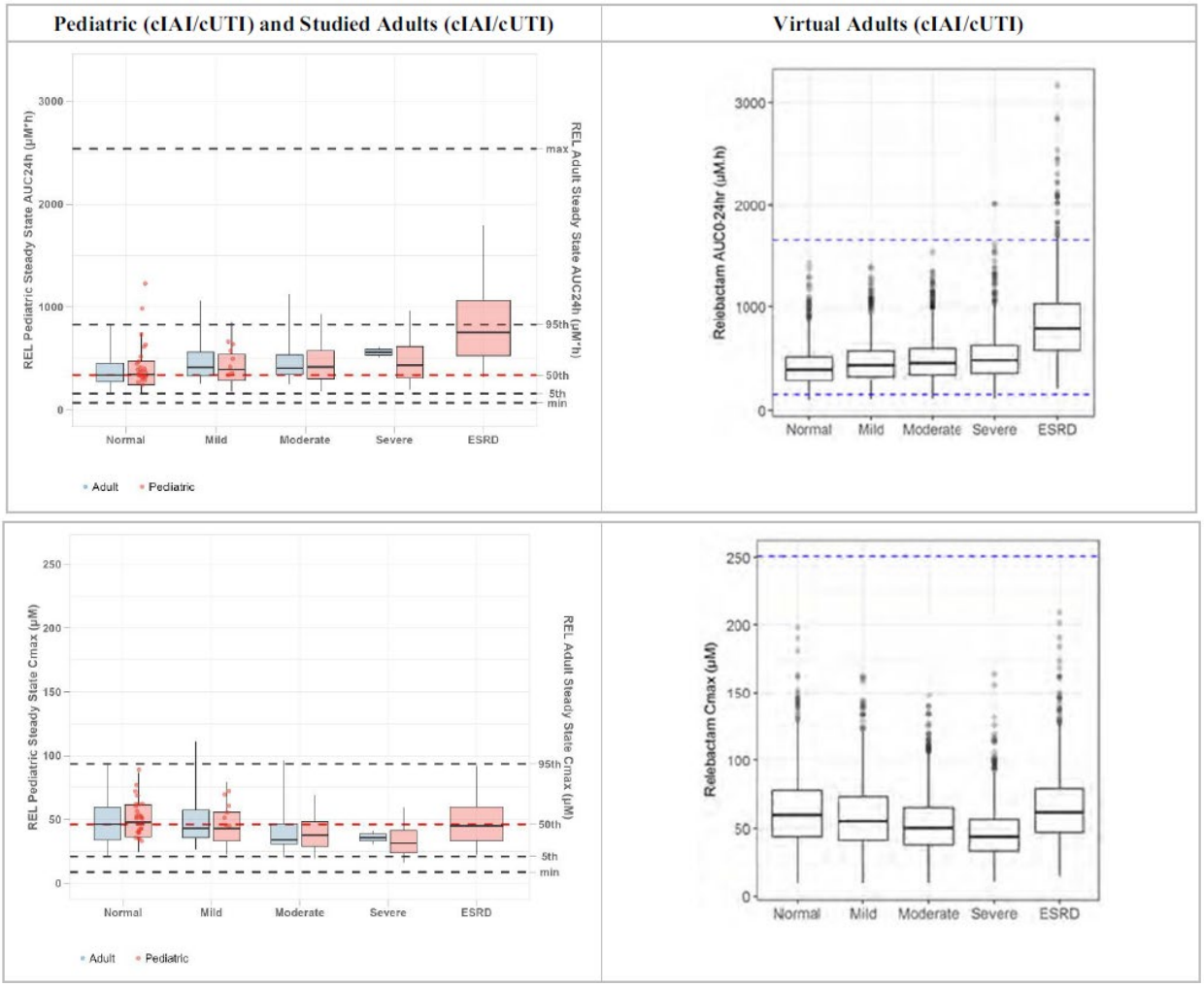
Figure 16. Comparison of Model-Simulated and EBE-Based Post-hoc Imipenem Steady-State PK Exposures (AUC0-24h in Top Panel; Cmax in Bottom Panel) Between cIAI/cUTI Pediatric RI Population (≥30 kg and < 18 Years of Age) and cIAI /cUTI Adult RI Population



Notes: Red box plots represent simulated virtual RI pediatric exposures using N=3155 virtual pediatric population received recommended renal function adjusted IMI/REL dosing regimen; red circles represent individual post-hoc exposures in studied pediatric patients (P020 and P021) following the protocol-defined dosing regimen; blue box plots represent individual post-hoc exposures obtained from studied

adult patients receiving approved renal function adjusted IMI/REL dosing regimen; white boxplots represent simulated virtual cIAI/cUTI RI adult exposures using N=1000 virtual adult population receiving approved renal function adjusted IMI/REL dosing regimen; For these boxplots the area represents the interquartile interval, the thick black line represents median, and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Data beyond the end of the whiskers are called "outlying" points. Horizontal dashed and dotted lines in the left panels represent corresponding distribution of the studied adult post-hoc exposures from Phase 2/3 studies for cIAI/cUTI. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. The blue horizontal dashed lines in the right panels represent the upper and lower clinical bound of exposure as determined in the adult analysis.
Source: Applicant's response to Information Request (SDN 622), Figure 3, pages 9 - 10.

Figure 17. Comparison of Model-Simulated and EBE-Based Post-hoc REL Steady-State PK Exposures (AUC0-24h in Top Panel; Cmax in Bottom Panel) Between cIAI/cUTI Pediatric RI Population (≥30 kg and < 18 Years of Age) and cIAI /cUTI Adult RI Population



Notes: Red box plots represent simulated virtual RI pediatric exposures using N=3155 virtual pediatric population received recommended renal function adjusted IMI/REL dosing regimen; red circles represent individual post-hoc exposures in studied pediatric patients (P020 and P021) following the protocol-defined dosing regimen; blue box plots represent individual post-hoc exposures obtained from studied

adult patients receiving approved renal function adjusted IMI/REL dosing regimen; white boxplots represent simulated virtual cUTI/cIAI RI adult exposures using N=1000 virtual adult population receiving approved renal function adjusted IMI/REL dosing regimen; For these boxplots the area represents the interquartile interval, the thick black line represents median, and the lower and upper whiskers extend to the 5th and 95th percentiles of the distribution. Data beyond the end of the whiskers are called "outlying" points. Horizontal dashed and dotted lines in the left panels represent corresponding distribution of the studied adult post-hoc exposures from Phase 2/3 studies for cIAI/cUTI. Minimum (black), 5th (black), 50th (red), 95th (black), and maximum (black) are shown. The blue horizontal dashed lines in the right panels represent the upper and lower clinical bound of exposure as determined in the adult analysis
Source: Applicant's response to Information Request (SDN 622), Figure 4, pages 11 - 12.

Table 43. Imipenem Population PK Derived Geometric Mean (CV%) Exposures (AUC0-24h and Cmax) at Steady-State in Virtual Pediatric RI Population (≥30 kg and <18 Years) Following Recommended Renal Function Adjusted IMI/REL Dosing Regimen Administration and in Virtual Adult Patients Following Approved Renal Function Adjusted IMI/REL Dosing Regimen Administration

	Imipenem							
	Adults (cIAI/cUTI)		Adults (HABP/VABP)		Pediatric (cIAI/cUTI)		Pediatric (HABP/VABP)	
Renal category	AUC 0-24hr (μM-*hr)	Cmax (μM)	AUC 0-24hr (μM*hr)	Cmax (μM)	AUC 0-24hr (μM*hr)	Cmax (μM)	AUC 0-24hr (μM*hr)	Cmax (μM)
ESRD	619.3 (57.4)	65.2 (59.8)	1140.2 (61.5)	124.5 (59.1)	703.7 (43.9)	55.6 (37.9)	1127.6 (44.9)	90.1 (38.1)
Severe	437.2 (56.4)	52.9 (60.1)	757.0 (59.9)	96.7 (59.3)	480.4 (42.0)	46.5 (38.1)	781.0 (41.3)	75.9 (36.9)
Moderate	475.0 (57.1)	66.9 (61.7)	806.2 (61.8)	119.8 (62.8)	530.8 (41.6)	62.3 (38.1)	854.6 (41.3)	101.0 (38.0)
Mild	501.9 (56.2)	79.4 (61.8)	818.4 (59.5)	140.8 (61.4)	556.5 (41.0)	76.8 (38.6)	906.0 (40.5)	125.1 (38.0)
Normal	500.0 (56.3)	88.9 (62.1)	812.2 (59.4)	159.1 (62.3)	542.7 (41.4)	89.5 (38.8)	874.2 (40.8)	144.2 (37.7)

N is 1000 for each RI category in adults; N is 3155 for each RI category in pediatrics.
Source: Applicant's response to Information Request (SDN 622), Table 2, page 17.

Table 44. REL Population PK Derived Geometric Mean (CV%) Exposures (AUC0-24h and Cmax) at Steady-State in Virtual Pediatric RI Population (≥30 kg and <18 Years) Following Recommended Renal Function Adjusted IMI/REL Dosing Regimen Administration and in Virtual Adult Patients Following Approved Renal Function Adjusted IMI/REL Dosing Regimen Administration

	Relebactam							
	Adults (cIAI/cUTI)		Adults (HABP/VABP)		Pediatric (cIAI/cUTI)		Pediatric (HABP/VABP)	
Renal category	AUC 0-24hr (μM*hr)	Cmax (μM)	AUC 0-24hr (μM*hr)	Cmax (μM)	AUC 0-24hr (μM*hr)	Cmax (μM)	AUC 0-24hr (μM*hr)	Cmax (μM)
ESRD	780.0 (43.8)	61.2 (41.2)	1652.0 (53.7)	126.0 (49.8)	754.3 (55.8)	44.6 (45.6)	1310.9 (57.0)	73.1 (47.5)
Severe	479.0 (43.8)	43.3 (41.8)	905.1 (49.4)	76.8 (44.8)	433.3 (52.1)	31.1 (41.4)	767.5 (51.2)	50.2 (41.3)
Moderate	452.4 (44.7)	49.0 (43.1)	826.5 (49.5)	80.6 (43.9)	416.5 (51.9)	37.1 (39.9)	728.4 (51.2)	57.8 (40.3)
Mild	432.2 (44.3)	54.7 (43.9)	736.8 (46.4)	83.9 (42.7)	391.7 (50.5)	42.6 (39.7)	695.2 (49.7)	65.7 (39.3)
Normal	390.5 (44.5)	58.5 (44.9)	655.2 (47.9)	87.6 (43.8)	341.3 (51.3)	47.0 (40.1)	597.3 (50.8)	70.5 (39.0)

N is 1000 for each RI category in adults; N is 3155 for each RI category in pediatrics.
Source: Applicant's response to Information Request (SDN 622), Table 3, page 18.

15.3.1.5. Listing of analyses codes and output files

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the reviewer's final model	**Imipenem**: intpoppk0p020p021-c2num.csv **Relebactam**: intpoppk0p020p021-c2num.csv	**Imipenem**: Reviews\Ongoing PM Reviews\Imipenem_relebactam_NDA212819_XP\Imipenem\ intpoppk0p020p021-c2num.csv **Relebactam**: Reviews\Ongoing PM Reviews\Imipenem_relebactam_NDA212819_XP\Relebactam\ intpoppk0p020p021-c2num.csv
NONMEM code for the reviewer's final model	**Imipenem**: run1509.mod **Relebactam**: run2509.mod	**Imipenem**: Reviews\Ongoing PM Reviews\Imipenem_relebactam_NDA212819_XP\Imipenem\ run1509.mod **Relebactam**: Reviews\Ongoing PM Reviews\Imipenem_relebactam_NDA212819_XP\Relebactam\ run2509.mod

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/s/

MARK S NEEDLES
12/09/2025 11:58:37 AM

DMITRI IARIKOV
12/09/2025 12:02:01 PM
Avery Goodwin signed on behalf of Kerian Grande Roche Scott Komo signed on behalf of Daniel Rubin Dorota Matecka signed on behalf of George Lunn