11 December 2025
EMADOC-1700519818-2608679
Committee for Medicinal Products for Human Use (CHMP)

CHMP Assessment report

Recarbrio

International non-proprietary name: imipenem / cilastatin / relebactam

Procedure No. EMA/VR/0000265089

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}24hr}$	area under the plasma concentration-time curve from zero to 24 hours
AUC/MIC	area under the plasma concentration-time curve normalised by the minimum inhibitory concentration
BLI	β-lactamase inhibitor
CDC	Centers for Disease Control and Prevention
CI	confidence interval
cIAI	complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institute
CR	carbapenem-resistant
CrCl	creatinine clearance
CSR	Clinical Study Report
cUTI	complicated urinary tract infection
CYP	cytochrome P450
DDI	drug-drug interaction
ECI	event of clinical interest
EFU	early follow-up
EMA	European Medicines Agency
EOT	end of therapy
ESBL	extended spectrum β-lactamase
ESRD	end –stage renal disease
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
*f*AUC/MIC	unbound area under the plasma concentration-time curve normalised by the minimum inhibitory concentration
$fAUC_{0\text{-}24hr}$	unbound area under the plasma concentration-time curve from zero to 24 hours
$fAUC_{0\text{-}24hr}$/MIC	unbound area under the plasma concentration-time curve from zero to 24 hours normalised by the minimum inhibitory concentration
*f*T>MIC	time unbound concentration is above the minimum inhibitory concentration
FDC	fixed-dose combination
GCP	Good Clinical Practice
HABP	hospital-acquired bacterial pneumonia
IAI	intra-abdominal infection
ICU	intensive care unit
IMI	imipenem/cilastatin
IMI/REL	fixed-dose combination of imipenem/cilastatin/relebactam (MK-7655A)
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
MATE	multidrug and toxin extrusion protein
MDR	multi-drug resistant
ME	microbiologically evaluable

MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration at which half 50% of isolates inhibited
MIC_{90}	minimum inhibitory concentration at which half 90% of isolates inhibited
Mate	microbiological intent-to-treat
mMITT	microbiological modified intent-to-treat
OAT	organic anion transporter
P	p-value
PD	pharmacodynamic
PDC	pyruvate dehydrogenase complex
PK	pharmacokinetic(s)
PSUR	periodic safety update report
PTA	probability of target attainment
REL	relebactam (MK-7655)
SAE	serious adverse event
SmPC	Summary of Product Characteristics
t1/2	terminal half-life
ULN	upper limit of normal
US	United States
V1	central volume of distribution
VABP	ventilator-associated bacterial pneumonia

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 07 April 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to extend the approved adult indications for RECARBRIO to include treatment of paediatric population from birth to <18 years of age, based on final results from two paediatric studies (MK-7655A-021 and MK-7655A-020); phase 2/3 study MK-7655A-021 addressed safety, tolerability, efficacy and PK, and phase 1b study MK-7655A-020 addressed PK, safety, and tolerability of MK-7655A in paediatric subjects from birth to less than 18 years of age with confirmed or suspected gram-negative infections. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and implement minor editorial corrections.

The variation requested amendments to the Summary of Product Characteristics, to the Package Leaflet, and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0190/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0190/2024 was completed.

The PDCO issued an opinion on compliance for the PIP P/0190/2024.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Alar Irs

Timetable	Actual dates
Submission date:	07 April 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	19 June 2025
CHM Co-Rapporteur's preliminary assessment report circulated on:	03 July 2025
Joint Rapporteur's updated assessment report circulated on:	17 July 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2025
MAH's responses submitted to the CHMP on:	08 September 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	14 October 2025
PRAC RMP advice and assessment overview adopted by PRAC	30 October 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	06 November 2025
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	13 November 2025
MAH's responses submitted to the CHMP on:	18 November 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 November 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	04 December 2025
CHMP opinion:	11 December 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Treatment of infections due to aerobe Gram-negative microorganisms in adults with limited treatment options.

State the claimed the therapeutic indication

Recarbrio is indicated ***in adult and paediatric patients*** for:

- Treatment of hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP) ~~in adults~~ (see sections 4.4 and 5.1).

- Treatment of bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP ~~in adults~~.
- Treatment of infections due to aerobic Gram-negative organisms ~~in adults~~ with limited treatment options (see sections 4.2, 4.4, and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Epidemiology

MDR gram-negative bacteria, especially ESBL-producing organisms and CR organisms, are a worldwide problem in both adult and paediatric patients. MDR pathogens are commonly observed in LRTI including HABP and VABP, cIAI, and cUTI. These infections are difficult to treat and are associated with high direct medical costs (including longer hospital stays) in paediatric patients. They are also associated with high levels of morbidity and mortality in paediatric patients, with a reported mortality of up to 50% for some infections[1].

Aetiology and pathogenesis

MDR gram-negative bacterial infections are difficult to treat and are associated with longer hospital stays in paediatric patients.

Hospital acquired pneumonia /Ventilator acquired pneumonia

Paediatric patients experience significant morbidity and mortality due to HABP and VABP, particularly in the PICU. In a multicenter observational study of 862 children in the US, a HABP/VABP incidence of 1.9 cases per 1000 PICU days and a VABP incidence rate of 3.9 cases per 1000 ventilator-days were observed[2]. Neonates have been shown to be particularly vulnerable to VABP, with a reported incidence of 15.8 cases per 100 mechanically ventilated neonates[3]. Children with VABP are almost 3 times more likely to die compared with mechanically ventilated children without VABP[4].

Aside from *Staphylococcus aureus*, the most common pathogens responsible for paediatric HABP/VABP are *Pseudomonas aeruginosa* and *Enterobacterales*.

Data from the US and EU have shown that appendicitis is overwhelmingly the most common cause of paediatric cIAIs, with an annual incidence rate from 1 to 2 per 10,000 children between birth and 4 years of age to 19 to 28 per 10,000 children younger than 14 years[5]. The mortality rate in patients with severe IAIs have been reported as being as high as 50%[6].

---

[1] Dong SW, Sharma TS, Sue PK. Approach to multidrug resistant infections in pediatric transplant recipients. Front Pediatr. 2023 Dec 7;11:1270564.
Chiotos K, Tamma PD, Flett KB, Karandikar MV, Nemati K, Bilker WB, et al. Increased 30-day mortality associated with carbapenem-resistant Enterobacteriaceae in children. Open Forum Infect Dis. 2018:ofy222.
Romandini A, Pani A, Schenardi PA, Pattarino GAC, De Giacomo C, Scaglione F. Antibiotic resistance in pediatric infections: global emerging threats, predicting the near future. Antibiotics. 2021 Apr 6;10:393.
[2] Ericson JE, McGuire J, Michaels MG, Schwarz A, Frenck R, Deville JG, et al. Hospital-acquired pneumonia and ventilator-associated pneumonia in children: a prospective natural history and case-control study. Pediatr Infect Dis J. 2020 Aug;39(8):658- 64
[3] Dell'Orto V, Raschetti R, Centorrino R, Montane A, Tissieres P, Yousef N, et al. Short- and long-term respiratory outcomes in
neonates with ventilator-associated pneumonia. Pediatr Pulmonol. 2019;54:1982-8.
[4] Bradley JS. Considerations unique to pediatrics for clinical trial design in hospital-acquired pneumonia and ventilator-associated pneumonia. Clin Infect Dis. 2010 Aug 1;51 Suppl 1:S136-43.
Gupta S, Boville BM, Blanton R, Lukasiewicz G, Wincek J, Bai C, et al. A multicentered prospective analysis of diagnosis, risk factors, and outcomes associated with pediatric ventilator- associated pneumonia. Pediatr Crit Care Med. 2015 Mar;16(3):e65-73.
[5] Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990 Nov;132(5):910-25.
[6] Napolitano LM. Intra-abdominal infections. Semin Respir Crit Care Med. 2022;43(1):10-27.

Complicated intraabdominal infections

cIAI arising from the lower GI tract is likely to be polymicrobial in nature. Large bowel infections are often caused by facultative and obligate anaerobic organisms, including gram-negative organisms such as Enterobacterales and *P aeruginosa* and gram-positive organisms such as *Enterococci* and *Streptococci*. In a study of 100 paediatric patients with ruptured appendices, the predominant aerobic gram-negative bacteria were *Escherichia coli* and *P aeruginosa*, and the most common anaerobic bacteria were gram negative bacilli (*Bacteroides fragilis* group and *Fusobacterium* spp.) and gram-positive anaerobic cocci (*Clostridioides* spp.)[7]. Nosocomially acquired pathogens associated with a high degree of antibiotic resistance include strains of *P aeruginosa*, *Serratia marcescens*, *Acinetobacter*, and *Providencia* spp. Furthermore, drug-resistant pathogens such as ESBL-producing *Enterobacterales*, methicillin-resistant *S aureus*, and vancomycin-resistant *Enterococci* may present in cIAI[8].

Complicated urinary tract infections

UTIs are among the most common infections diagnosed in paediatric patients. cUTIs are associated with an increased likelihood of drug resistance in the infecting microorganisms, which can further complicate treatment and lead to high mortality rates. In a retrospective study conducted in Turkey, of 344 paediatric outpatients diagnosed with UTI due to *E coli* and *Klebsiella*, ESBL-producing bacteria were isolated from 148 (43%) of the patients, and all of these had at least 1 episode of pyelonephritis[9].

Clinical presentation, diagnosis

Infections typically caused by aerobe Gram-negative organisms (cUTI, cIAI and HABP/VABP) are diagnosed based on clinical presentations and radiologic imaging in addition to microbiological investigations to characterise the pathogens causing the infections.

Management

Treatment of Gram-negative infections in paediatric patients includes consideration of such factors as the site and severity of infection and recent prior antibacterial use. For empiric treatment of bacterial nosocomial pneumonia, an IV antibacterial regimen that includes coverage of gram-negative bacilli and gram-positive organisms should be used with specific choice of agent based on the local patterns of resistance. A carbapenem or BL plus a BLI should ideally be used where ESBL-producing *Enterobacterales* are endemic. The treatment of cIAI involves a multifaceted approach, including a source-control procedure to drain/remove infected foci and control ongoing peritoneal contamination, as well as adjunctive antimicrobial treatment. As cIAI is associated with mixed aerobic and anaerobic bacteria, appropriate antimicrobial therapy should include either a single agent with a broad antibacterial spectrum or combination therapy. Empiric antimicrobial therapy for cUTI should have a sufficiently broad spectrum of activity to cover the most commonly isolated pathogens. Targeted therapy should be given once urine culture and susceptibility results are available.

Despite the availability of multiple antibiotics for use in the treatment of HABP/VABP, cIAI, and cUTI, in paediatric patients, the emergence and global spread of resistant pathogens have created an unmet

[7] Brook I. Bacterial studies of peritoneal cavity and postoperative surgical wound drainage following perforated appendix in children. Ann Surg. 1980 Aug;192(2):208-12.
[8] Dupont H. The empiric treatment of nosocomial intra-abdominal infections. Int J Infect Dis. 2007 May;11 Suppl 1:S1-6.
[9] Kizilca O, Siraneci R, Yilmaz A, Hatipoglu N, Ozturk E, Kiyak A, et al. Risk factors for community-acquired urinary tract infection caused by ESBL-producing bacteria in children. Pediatr Int. 2012;54:858-62.

medical need for safe and effective alternative agents. Few broad-spectrum antibacterial agents are formally approved for use in paediatric patients.

2.1.2. About the product

Recarbrio consists of a fixed-dose combination of imipenem (IMI), cilastatin (CIL) and relebactam (REL).

Imipenem (IMI) is a carbapenem β-lactam antibacterial agent that inhibits bacterial cell-wall synthesis by targeting penicillin-binding proteins (PBPs). It has a spectrum that includes Gram positive, Gram negative and anaerobic bacteria. Cilastatin (CIL) is a renal dehydropeptidase inhibitor that limits the renal metabolism of IMI. CIL does not have antibacterial activity. Imipenem-cilastatin has been authorised and used in the EU since the 1980s. It is given intravenously at doses up to 1 g q6h.

Relebactam (REL) is a diazabicyclooctane β-lactamase inhibitor that inhibits a variety of Ambler class A and C but not class B and D β-lactamases. REL has, in itself, no significant antibacterial activity at clinically relevant doses. The role of REL in the FDC is to restore the activity of IMI in IMI-resistant gram-negative infections when the resistance is caused by production of β-lactamases within the spectrum of REL´s inhibitory activity. IMI/REL was approved in the EU in February 2020 for the treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options. Subsequently, in November 2020, IMI/REL was approved in the EU for use in adults for the treatment of HABP (including VABP) and bacteraemia that occurs in association with, or is suspected to be associated with, HABP or VABP.

IMI/REL is provided in a single vial as 500 mg imipenem/500 mg cilastatin/250 mg REL for IV infusion.

A large susceptibility surveillance study of gram-negative bacteria isolates from paediatric patients, which collected data from 2015 to 2017 from 221 laboratories in 59 countries, demonstrated that the incidence of MDR non-*Morganellaceae Enterobacterales* (NME) was similar for both paediatric patients (21.7%) and adults (25.6%)[10]. Similarly, 18% of *P aeruginosa* isolates from paediatric patients were MDR. Imipenem/REL inhibited >97% of NME and 94.2% of isolates of *P aeruginosa* from paediatric patients in this study. Among highly resistant organisms, all KPC–positive isolates, 93.3% of MDR isolates, and 70.5% of MDR *P aeruginosa* isolates from paediatric patients were susceptible to imipenem/REL.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

An initial PSP was agreed to by the FDA on 18-DEC-2015. An initial PIP was agreed to with the PDCO on 15-JUN-2016 and subsequently modified 4 times. Scientific Advice has not been sought on the paediatric development programme.

2.1.4. General comments on compliance with GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

[10] Karlowsky JA, Lob SH, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem/relebactam against gram-negative bacilli from pediatric patients-study for monitoring antimicrobial resistance trends (SMART) global surveillance program 2015- 2017. J Pediatric Infect Dis Soc. 2021 Mar;10(3):274-81.

2.2. Quality aspects

The variation does not include any specific quality variation application. The already approved formulation, powder for solution for infusion, intended for adults is suggested to be used also for children from birth up to 18 years of age.

The only excipient included is sodium hydrogen carbonate and the powder is to be constituted and further diluted in 0.9% sodium chloride or in 5% glucose using a 100 ml infusion bag. The sodium content to be administered is within acceptable amounts and no safety concerns are foreseen. The handling of the constitution and dilution procedure is sufficient described in the SmPC. For children from 2 kg to less than 30 kg low volumes will be administered and to mitigate the risk of an overdose instructions to remove amounts not to be used from the 100 ml of infusion solution are given in the SmPC.

From a quality point of view, the proposed formulation is considered acceptable to be used in children from birth up to 18 years of age.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. A discussion for the new proposed indication based on the pre-existing non-clinical package of Recarbrio (EMEA/H/C/004808, approved in 2020) has been provided as a Non-clinical Overview. No new study assessment is provided in this procedure. Additionally, some text from the Recarbrio EPAR is also included below as supplementary information. The Recarbrio non-clinical dossier provided the most in-depth assessment for REL. The IMI non-clinical safety profile has been well characterised in support of medical products Primaxin and Tienam. IMI has also a long history of safe use in adults and children for the treatment of the multiple serious bacterial infections, including cUTI and cIAI.

2.3.1. Introduction

Recarbrio contains three active substances: imipenem (IMI), relebactam (REL) and cilastatin sodium (CIL). IMI and REL are a β-lactam/β-lactamase inhibitor combination. CIL is an inhibitor of the renal dipeptidase, dehydropeptidase l. CIL was developed to prevent the renal metabolism of IMI.

2.3.2. Pharmacology

No new nonclinical pharmacology studies have been conducted to support the use of IMI/CIL/REL in the intended paediatric patient population. It can be noted that a secondary pharmacology off-target screen for REL (10-100 um) against 163 biomolecular targets did not identify any possible off-targets.

Safety pharmacology

For the safety pharmacology, there were no REL related effects of concern in the clinically relevant dose range on cardiovascular, respiratory or CNS functions observed in the safety pharmacology in-vivo models. IMI and CIL alone and in combination were evaluated in cardiovascular, respiratory, central nervous system and gastrointestinal system pharmacology studies. No cardiovascular or respiratory effects of concern were reported in these studies. CNS related findings as seizures and convulsion-like activity were observed in the safety pharmacology studies of IMI in rabbit and rat at approximately 6 -10 times the maximum recommended daily human dose in IMI/CIL/REL product (the convulsions reported in a repeat-dose toxicity study in rats conducted after the initial filing for IMI-

CIL). CIL alone had no significant actions on the central nervous system. It can be noted that as also reported in the SmPC of Tienam, CNS adverse reactions, such as seizures, confusional states and myoclonic activity, have also been reported in humans treated with IMI/CIL, when recommended dosages of IMI imipenem were exceeded. IMI and CIL alone or in combination had no effects of concern in the safety pharmacology evaluating the gastrointestinal system.

Pharmacodynamic drug interactions

2.3.3. Pharmacokinetics

No new nonclinical pharmacokinetic studies have been conducted to support the use of IMI/CIL/REL in the intended paediatric patient population.

Regarding REL, it showed a low plasma clearance (6.2, 12.4, 3.4 and 5.3 ml/min/kg), a small volume of distribution (0.3-0.4 L/kg) and a short half-life (0.9, 0.5, 1.2, and 0.8 hr) in the four preclinical species tested. Overall, REL undergoes minimal metabolism in nonclinical species and in humans (<10% of the dose) and is cleared primarily via renal excretion as unchanged drug by glomerular filtration with involvement of active tubular secretion (~30% in human), thus it is not expected to be subject to DDI when co-administered with CYP inhibitors or inducers. REL is a substrate of renal transporters (OAT3, OAT4, MATE1 and MATE2K). Given that active secretion accounts for only ~30% of the total clearance of REL, REL is unlikely to be subject to clinically meaningful DDIs when co-administered with inhibitors of these renal transporters. Metabolism of IMI was shown to occur primarily in the kidney. The major pathway of metabolism of IMI is by hydrolysis of the beta-lactam ring by the enzyme known as dehydropeptidase-I localised on the brush-border of proximal renal tubular epithelium. The renal metabolic degradation results in a low urinary recovery of intact IMI in nonclinical species and in humans. IMI exhibited a low-to-moderate plasma clearance (ranging from 6.23 mL/min/kg in dogs to 33.0 mL/min/kg in rabbits), and a short half-life (<1 hr) in nonclinical species. CIL undergoes metabolism in nonclinical species and humans to various extent, ranging from 85% in rabbits to <25% in humans. The pharmacokinetic profile of CIL indicated a half-life almost identical to that of IMI, supporting the co-administration.

Regarding distribution, in a QWBA study, rat tissues with the highest concentrations of REL radioactivity at T_{max} were kidney cortex, kidney medulla, urinary bladder, oesophagus, blood, non-pigmented skin, aorta, oral mucosa, lung, and eye uveal tract, ranging from 29 to 315 µg equiv/g. The highest overall concentration of radioactivity was found in the urinary bladder contents (~932 µg equiv/g at 0.5 hr), consistent with renal excretion being the major elimination route. Brain, seminal vesicles, eye lens and bone were among the tissues with lowest concentrations of radioactivity (<1.5 µg equiv/g at T_{max}). The low levels of radioactivity in the brain suggests REL is not prone to pass the blood brain barrier. The tissue concentration versus time profiles showed that radioactivity in tissues declined rapidly, consistent with the short half-life of the compound. In rats following intravenous administration of radiolabelled IMI, radioactivity was distributed primarily in the kidney, consistent with renal excretion being the elimination route. The disappearance of radioactivity in tissues parallels the disappearance profile from plasma. Tissue distribution of CIL in rats revealed no accumulation of radioactivity in any of the tissues, and the concentration of radioactivity in tissues appears to decrease in parallel with the disappearance profile of plasma radioactivity.

[3H]REL displayed a low binding (~78-90% mean unbound) to mouse, rat, monkey, and human plasma proteins. Plasma protein binding was independent of REL concentration at 5 and 50 µM in all species. The equilibrium blood-to-plasma concentration ratio was ~0.6 in all tested species (mouse, rat, monkey, and human), indicating that REL does not preferentially distribute into red blood cells.

The binding of IMI and CIL to human serum proteins is low (~20% and ~40%, respectively). Placental transfer of REL was investigated in pregnant Sprague-Dawley rats and New Zealand White rabbits, and the results suggest that REL has the ability to cross the placenta in both species, with the foetal plasma levels representing ~3-6% of the maternal plasma levels.

2.3.4. Toxicology

No new nonclinical safety studies have been conducted to support the paediatric indication. Previously assessed for REL were repeat-dose IV toxicity studies in Wistar Han rats and cynomolgus monkeys of up to 3-months duration, a standard genotoxicity battery, and a series of DART studies in mice, rats and/or rabbits. An exploratory juvenile range-finding study and a pivotal JAS were conducted in rats to support initiation of paediatric clinical trials. The toxicity of REL when co-administered with IMI was evaluated in a 1-month study in monkeys (monkeys were approximately 2 years old in age, equivalent to an adolescent human).

Repeat dose toxicity

The kidney was identified as a target organ for toxicity of REL in both rat and monkey and the CNS was a target organ in rat.

In rats, minimal to mild cytoplasmic granularity in the renal tubular epithelium was observed in all animals exposed to daily doses of REL for 3 months (65, 150, and 300 mg/kg/day). No evidence of necrotic or degenerative changes was observed (no recovery period included in the studies). In the 1-month repeat dose toxicity study in monkeys, the highest dose of REL, 225 mg/kg/day, induced an increase in kidney weight by 36% (actual weight and related to body and brain weight). In 2 of 6 animals very slight tubule epithelium degeneration was observed and very slight to slight granular cytoplasm in the tubule epithelium in all animals in the group. One female individual in the group also had increased urea nitrogen and creatinine as well as fine granular casts and hyaline casts in the urine. In the three months monkey study, the animals were administered 150 mg/kg/day at a maximum. A dose level at which minimal to mild cytoplasmic granularity in the tubular epithelium was observed.

CNS findings (clinical signs, but no histopathological findings) were also observed in rats dosed with REL in the 1-month and 3-month studies at doses achieving very high C_{max} concentrations. These included convulsion-like activity and tremors which are likely indicative of a central nervous system effect of REL. However, it can be noted that nonhuman primates dosed with IMI/REL in combination at clinically relevant exposures showed no evidence of CNS-related physical signs.

Genotoxicity and carcinogenicity

The outcome of the genotoxicity studies for REL was negative. No carcinogenicity tests have been conducted. IMI and CIL (alone and in combinations) were also negative in standard battery of in vitro and in vivo genetic toxicity studies (including V79 mammalian cell mutagenesis assay and unscheduled DNA synthesis assay). No carcinogenicity studies were conducted with IMI/CIL.

Reproduction toxicity

In the fertility studies in males and females, there were no REL-related effects on mating, fertility, or male reproductive assessments (sperm analysis). The NOAEL for male and female fertility is therefore ≥450 mg/kg/day, corresponding to an exposure margin of at least 8 times the human exposure based on AUC. There were no gross or microscopic changes in reproductive organs observed in repeat-dose

studies in rats and monkeys for up to 12 weeks of duration. No treatment-related effects on fertility are noted after IMI/CIL administration to male and female rats.

In mouse EFD, there was an apparent increase of skeletal malformations (1, 4, 3, and 5 foetuses in the control, 80, 200, and 450 mg/kg/day group). The highest dose tested (450 mg/kg/day), rendered a systemic exposure marginal between human and pregnant mice of 6.7x (based on $AUC_{0\text{-}24hr}$) and x31 (based on C_{max}). There were no toxic effects detected in a rat EFD (at 50, 150, and 450 mg/kg/day). The systemic exposure marginal between human and pregnant rat administered the highest dose 450 mg/kg/day was 8.4x (based on $AUC_{0\text{-}24hr}$) and x111 (based on C_{max}). For rabbit EFD, no treatment-related adverse effects were detected in the mothers except for an observation on discoloured urine which is thought to be due to excretion of a hydrolysis product of REL. A slight increase in the incidence of foetuses with either a malformation or variation of the hyoid bone was observed (M/V: 1/1, 0/2, 0/2, and 3/5 foetuses in the control, 35, 275, and 450 mg/kg/day group). The systemic exposure marginal between human and pregnant rabbit administered the highest dose 450 mg/kg/day was 29x (based on $AUC_{0\text{-}24hr}$) and x147 (based on C_{max}). A teratology study in pregnant cynomolgus monkeys given IMI-CIL at doses of 40/40 mg/kg/day (bolus intravenous injection) resulted in maternal toxicity including emesis, inappetence, body weight loss, diarrhoea, abortion, and death in some cases. When doses of imipenem-cilastatin sodium (approximately 100/100 mg/kg/day or approximately 3 times the maximum recommended daily human dose in a IMI/CIL/REL product) were administered to pregnant cynomolgus monkeys at an intravenous infusion rate which mimics human clinical use, there was minimal maternal intolerance (occasional emesis), no maternal deaths, no evidence of teratogenicity, but an increase in embryonic loss relative to control groups.

The potential effects of REL on development, growth, behaviour, reproductive performance, and fertility of F1 generation were evaluated in rats after administration of 0, 64, 200, and 450 mg/kg/day to F0 females from gestation day 6 through day 20 postpartum. Furthermore, the F1 pups were investigated for cohabitation on postnatal week (PNW) 12. Mean plasma exposure of REL for F0 females on gestational day 15 for the highest dose (450 mg/kg/day) was 3020 µMxhr which is 9.1x the human exposure at steady state. The REL concentration in milk or exposure in pups was collected from separate studies in rats. The foetal plasma levels were approximately 5% of the maternal plasma levels on gestation day 20 after administration of 450 mg/kg/day on GD7 through 20. In another study the ration of milk to maternal plasma concentration in rats was approximately 0.05 15 min post-dose.

In a rat JAV for REL (PNW 3 through PNW9 + 4w recovery) at 65, 200 and 450 mg/kg/day SC once daily between PND14 and PND34 followed by IV between PND35 to PNW9, there were no REL-related deaths, clinical observations, or effects on mean body weight, or food consumption, including no developmental changes in landmarks (vaginal opening, preputial separation), femur length, and no clinical signs or histo-morphologic findings up to the highest dose tested, 450 mg/kg/day (NOAEL, $AUC_{0\text{-}24hr}$ =2350 h*µM; C_{max}=3920 µM).

2.3.5. Ecotoxicity/environmental risk assessment

Three ERA documents have been provided; for REL, IMI and CIL.

Relebactam ERA

The original ERA for REL reached the Phase IIA stage and was approved as part of the initial MAA for RECARBRIO™ (EMEA/H/C/004808/0000) which was approved on 12 December 2019. Additional

indications have been added since, and a new CHMP ERA guideline became active 1 Sept 2024. With regards to exposure, the original PECsw approach was based on a maximum dose of 1,000 mg/day (250 mg every 6 hours) and a default market penetration (1% of population) and this remain valid for all expanded patient populations.

The provided ERA addressed the new technical requirements of the 2024 ERA-GL. The log Kow was below 3 and does not trigger PBT assessment in Phase I or bioconcentration/secondary poisoning assessment in Phase IIA. The highest Koc from sludge for REL was determined as 61.5 L/kg while the PECsw was 5 µg/L. This is insufficient to trigger a Phase IIB terrestrial assessment. A groundwater assessment via porewater is also not required. Relebactam is not effective as monotherapy, so it cannot be considered to be antimicrobial in itself. As such, no tailored assessment for antibiotics is deemed necessary.

As such, the conclusions in the present ERA that there is no environmental risk identified are supported.

Table 1 ERA overview table – Phase I

Substance (INN/Invented Name):	relebactam (MK-7655)		
CAS-number (if available):	1174020-13-3		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	Log K_{ow} < -2.0 (pH 5 to pH9)	The mean partition coefficient of the test substance for pH 5, 7 and 9 was determined to be <0.0100 for all pH (log Kow<-2.00). Potential PBT: *N*
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Kow	Log K_{ow} <-2.0	not B
Persistence	Ready biodegradability	N	NA
	DT50 Values are derived from the OECD 308 and have been recalculated to 12°C	DT50, water = 36-81*d DT50, sediment = 60-100d DT50, whole system = 43-88d	P
Toxicity	$NOEC_{aquatic}$	*670 ug/L*	Not T
PBT/vPvB statement:	Imipenem Monohydrate is considered to be not PBT, nor vPvB		
Phase I			
Parameter	Value	Unit	Conclusion

Phase I			
PEC_{sw},	5	µg/L	≥ 0.01 threshold: *Y*
Other concerns (e.g. chemical class)	Antibiotic drug, Requires tailored risk assessment.		Y

Table 2 ERA overview table – Phase II

Phase II Physical-chemical properties and fate			
			Remarks
Water solubility	OECD 105	55.9 g/L (pH 5) 63.3 g/L (pH 7) 76.0 g/L (pH 9)	
Adsorption-Desorption Soil 1 (DU) = Loam	OECD 106	$K_{d,\ soil\ 1}$ = 1.71 L/kg_{oc} log $K_{d,\ soil\ 1}$ = 0.232 $K_{oc,\ soil\ 1}$ = 26.5 L/kg_{oc} log $K_{oc,\ soil\ 1}$ = 1.42	oc: 6.45 %
Soil 2 (RMN) = Loamy Sand		$K_{d,\ soil\ 2}$ = 0.555 L/kg_{oc} log $K_{d,\ soil\ 2}$ = 0.00 $K_{oc,\ soil\ 2}$ = 68.2 L/kg_{oc} log $K_{oc,\ soil\ 2}$ = 1.83	oc: 0.81 %
Soil 3 (MSL) = Sandy Loam		$K_{d,\ soil\ 3}$ = 1.29 L/kg_{oc} log $K_{d,\ soil\ 3}$ = 0.110 $K_{oc,\ soil\ 3}$ = 65.2 L/kg_{oc} log $K_{oc,\ soil\ 3}$ = 1.81	oc: 1.98 %
Soil 4 (CA) = Clay		$K_{d,\ soil\ 4}$ = 1.64 L/kg_{oc} log $K_{d,\ soil\ 4}$ = 0.214 $K_{oc,\ soil\ 4}$ = 202 L/kg_{oc} log $K_{oc,\ soil\ 4}$ = 2.30	oc: 0.81 %
Sludge 1 (Wareham Sludge)		$K_{d,\ sludge\ 1}$ = 21.9 L/kg_{oc} log $K_{d,\ sludge\ 1}$ = 1.34 $K_{oc,\ sludge\ 1}$ = 61.5 L/kg_{oc} log $K_{oc,\ sludge\ 1}$ = 1.78	oc: 35.61 %
Sludge 2 (New Bedford Sludge)		$K_{d,\ sludge\ 2}$ = 6.49 L/kg_{oc} log $K_{d,\ sludge\ 2}$ = 0.786 $K_{oc,\ sludge\ 2}$ = 17.9 L/kg_{oc}	oc: 36.30 %

		log $K_{oc,\ sludge\ 2}$ = 1.38	
Ready Biodegradability Test	OECD 314B	Biodegradation half-life: 88d Elimination rate constant: 0.0079 day-1	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems, 101d. System 1 = *Tauton River* System 2 = *Wewantic River*	OECD 308	*Tauton/Weweantic River* DT50, water = 17-38d DT50, sediment = 28-47d DT50, whole system = 20-41d Corrected to 12 ℃: DT50, water = 36-81d DT50, sediment = 60-100d DT50, whole system = 43-88d % shifting to sediment >10% CO_2 = 4.05% / 5.21% NER_{total} = 82.1% / 67.9% $NER_{type\ 1}$ = ND	Water layer DT50 used data though to d101. Sediment layer DT50 used data d14 to d101.

Phase II Aquatic effect studies

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC EC_{10} *EC_{50}*	12 21 86	*mg*/L *mg*/L *mg*/L	growth rate, 72h
Algae, Growth Inhibition Test/ *A. flos-aquae*	OECD 201	NOEC EC_{50}	0.67	*mg*/L	growth rate, 72h

			>11	*mg*/L	The highest concentration (11mg/L) was not statistically significant but 2 middle doses (1.8 & 4.6 mg/L) were statistically significant. The dose below 1.8 mg/L was 0.67 mg/L. The latter was used in the risk assessment.
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	<u>Survival & size:</u> NOEC LOEC EC10 <u>Repro</u>: NOEC LOEC EC10	 9.6 >9.6 >9.6 2.7 4.8 ND	 *mg*/L *mg*/L *mg*/L *mg*/L *mg*/L	Highest concentration 9.6 mg/L.
Fish, *ELS / Fathead minnow (Pimephales promelas)*	OECD *210*	NOEC LOEC	9.2 >9.2	mg/L mg/L	Highest test concentration 9.2 mg/L.
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10 EC50	96.3 >1000	mg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD *218*	Emergence NOEC NOECoc10 LOEC EC50	 18 94.7 31 NA	 mg/kg_{dw} mg/kg_{dw} mg/kg_{dw}	100 mg/kg dw (nominal) or 31 mg/kg dw (measured) was the highest concentration tested. OC: 1.9%

		DevRate NOEC LOEC EC50	 31 >31 NA	 mg/kg_{dw} mg/kg_{dw}	
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**	
STP	5.0 ug/L	9600 ug/L	5.2×10^{-4}	No risk	
Surface water	5.0 ug/L	67 ug/L	0.07	No risk	
Groundwater	1.25 ug/L	6.7 ug/L	0.19	No risk	
Sediment	0.053 mg/kg dw	94.7 mg/kg dw	0.056	No risk	

Imipenem ERA

The original ERA for IMI (under the 2006 CHMP ERA GL, reaching Phase IIA stage) was approved as part of the follow up measure to the initial MAA for RECARBRIO™ (EMEA/H/C/004808/0000) from 2019.

A full, tailored assessment for antibiotic substances is missing (OECD TG201 study) and a non-acceptable consumption-based Fpen/PECsw refinement approach is part of the most recent submitted ERA. As such, no final conclusion on the environmental risk of IMI can be made at this stage and a commitment has been provided to submit an updated ERA in the future.

Table 3 ERA overview table – Phase I

Substance (INN/Invented Name):	imipenem monohydrate		
CAS-number (if available):	74431-23-5		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential- log Kow	OECD 117	*< -1.02* at pH *6.8*	Potential PBT: *N*
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Kow	*< -1.02 at pH 6.8*	not B Secondary poisoning assessment not required.

Persistence	Ready biodegradability	N	potentially P
	DT50 Values are derived from the OECD 308 and have been recalculated to 12°C	DT50, water = 2.7-3.3 days DT50, whole system = 3.2-4.3 days	Sediment DT50 unclear.
Toxicity	$NOEC_{aquatic}$	*0.002* mg/L	T
PBT/vPvB statement:	Imipenem Monohydrate is considered to be not PBT, nor vPvB		

Phase I			
Parameter	Value	Unit	Conclusion
PEC_{sw}	10	µg/L	≥ 0.01 threshold: *Y*
Other concerns (e.g. chemical class)	Antibiotic drug, Requires tailored risk assessment.		Y

Table 4 ERA overview table – Phase II

Phase II Physical-chemical properties and fate			
			Remarks
Water solubility		> *10* mg/L	Cited value
Hydrolysis	OECD 111	Half-live (25C) pH 4: 3.7h pH 7: 4.0d pH 9: 70 min	
Adsorption-Desorption Soil 1 = *Silty Clay Loam*	OECD 106	$K_{d,\ soil\ 1}$ = *15.7* L/kg_{oc} $K_{foc,\ soil\ 1}$ = *284*L/kg_{oc}	
Soil 2 = Loamy Sand		$K_{d,\ soil\ 2}$ = *17.3* L/kg $K_{doc,\ soil\ 2}$ = *2160 L/kg_{oc}* $K_{foc,\ soil\ 2}$ = *2365 L/kg_{oc}*	Highest soil adsorption values to be used for PEC_{SED}.
Soil 3 = Sandy Loam		$K_{d,\ soil\ 3}$ = *16.0* L/kg_{oc} $K_{foc,\ soil\ 3}$ = *793* L/kg_{oc}	
Sludge 1		$K_{d,\ sludge\ 1}$ = *7.46* L/kg_{oc} $K_{foc,\ sludge\ 1}$ = *24* L/kg_{oc}	
Sludge 2		$K_{d,\ sludge\ 2}$ = *6.73* L/kg_{oc} $K_{foc,\ sludge\ 2}$ = *33* L/kg_{oc}	Kfoc 33 L/kg highest sludge adsorption value. Soil assessment not required.

Ready Biodegradability Test	OECD 301*B*	Biodegradation for imipenem was 28.9% by Day 28.	The test substance was not inhibitory to the inoculum at the concentration tested.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems, 100d. System 1 = Silty clay loam (*Brandywine Creek)* System 2 =Sand (Choptank River)	OECD 308	*Brandywine* *Creek/ Choptank* *River* DT50, water = 1.27-1.56 days DT50, sediment = >100 days* DT50, whole system = 1.49-2 days CO_2 = 54.5% / 57.2% NER_{total} = 35.7% / 27.8% $NER_{type\ 1}$ = ND *Corrected to 12 ℃:* DT50, water = 2.7-3.3 days DT50, sediment = >213 days* DT50, whole system = 3.2-4.3 days % shifting to sediment >10%	* While sediment estimates were generated, the data analysis for sediment DT50 values is not considered robust/suitable. As such, no definitive conclusion about sediment persistence can be drawn. It can be noted that the DT50 values can be further refined by taking into account the radioactivity in the extractable fraction but this is presently not part of the ERA.

Phase II Aquatic effect studies

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/*A. flos-aquae, 72h*	OECD 201	NOEC EC_{10}	2.0 2.9	*µg*/L *µg*/L	Growth rate EC_{10} 2.9 *µg*/L is used for RQ_{SW} and RQ_{GW}.
Algae, Growth Inhibition Test/ *R. subcapitata, 72h*	OECD 201	NOEC EC_{10}	74 000	*µg*/L	Growth rate

			>74 000	*µg*/L	
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	1100 0	*µg*/L	Highest test concentration
Fish, *ELS / Fathead minnow (Pimephales promelas)*	OECD *210*	NOEC	9400	*µg*/L	Highest test concentration
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10} EC_{15}	500 800	*µg*/L *µg*/L	Total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD *218*	NOEC	57.4 382. 67	*mg*/kg_{dw} *mg*/kg_{dw}	Highest test concentration Sediment oc = 1.5%. NOEC normalised to 10% o.c. gives ~383 mg/kg dw. AF= 100 gives 3.83 mg/kg dw
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**	
STP	100 µg/L	50 µg/L	2	Risk [A]	
Surface water	10 µg/L	0.29 µg/L	34.48	Risk [A]	
Groundwater	2.5 µg/L	0.029 µg/L	86.21	Risk [A]	
Sediment	2390 mg/kg_{dw}	3826.7 mg/kg_{dw}	0.62	No risk [A]	

[A] Risk characterisation values are preliminary as the final ERA for imipenem has yet to be submitted, assessed and approved.

Cilastatin ERA

The original ERA for CIL (under the 2006 CHMP ERA GL, reaching Phase IIA stage) was approved as part of the follow up measure to the initial MAA for RECARBRIO™ (EMEA/H/C/004808/0000) from 2019. The exposure values for CIL are based on the maximum dose of 2000 mg/day and a default Fpen of 0.01 (giving PECsw 10 ug/L) and are acceptable.

The CIL adsorption by activated sludge solids was found to be less than 10% at all practical solid:solution ratios and also the product of solid: solution ratio, and the adsorption distribution coefficient for each of the activated sludge solids for each of the tested ratios was below 0.1. As such, it is reasonable to assume that Kfoc, sludge is substantially less than 1,000 L/kg and that Phase IIB terrestrial and groundwater via porewater assessment is not triggered. As the log Kow value was <3, an evaluation of the potential for secondary poisoning is not needed. Cilastatin has no antibacterial activity itself, so no tailored assessment for antibiotics is deemed necessary.

Overall, the present modified CIL ERA document is in line with the 2024 CHMP ERA GL and it does not identify no environmental risks.

Table 5 ERA overview table – Phase I

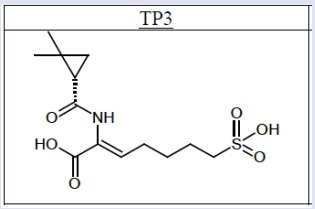
Substance (INN/Invented Name):	cilastatin		
CAS-number (if available):	82009-34-5		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	-2.00 (pH 4) -3.53 (pH 7) -4.18 (pH 9)	Potential PBT: *N*
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Kow	Log K_{ow} (pH 5 to pH9) <- 2.0	not B
Persistence	Ready biodegradability	NA	NA
	DT50 Values are derived from the OECD 308 and have been recalculated to 12°C	Not readily biodegradable but sediment half-lives not determined due to technical issues.	Not persistent in total system or water. Sediment undetermined.
Toxicity	$NOEC_{aquatic}$	*9.9 mg/L*	Not T
PBT/vPvB statement:	Cilastatin is considered to be not PBT, nor vPvB		

Phase I			
Parameter	Value	Unit	Conclusion
PEC_{sw}	10	µg/L	≥ 0.01 threshold: *Y*
Other concerns (e.g. chemical class)	Beta-lactamase inhibitor but without direct antibiotic activity.		No tailored risk assessment.

Table 6 ERA overview table – Phase II

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Hydrolysis	OECD 111	Half-live (25C) pH 4: 3.7h pH 7: 4.0d	

		pH 9: 70 min	
Adsorption-Desorption Soil 1 (TB-L-PF) = Silty Clay Loam	OECD 106	$K_{d, soil\ 1}$ = 1.45 L/kg $K_{oc, soil\ 1}$ = 30.9 L/kg Log $K_{f, soil\ 1}$ = 0.2215	oc: 4.70 %
Soil 2 (RMN-LS) = Loamy Sand		$K_{d, soil\ 2}$ = 1.59 L/kg $K_{oc, soil\ 2}$ = 198 L/kg Log $K_{f, soil\ 2}$ = 0.2434	oc: 0.80 %
Soil 3 (MSL-PF) = Sandy Loam		$K_{d, soil\ 3}$ = 2.24 L/kg $K_{oc, soil\ 3}$ = 132 L/kg Log $K_{f, soil\ 3}$ = 0.3774	oc: 1.70 %
Sludge 1 (Denton WWTP)		$K_{d, sludge\ 1}$ = ND $K_{oc, sludge\ 1}$ = ND Log $K_{f, sludge\ 1}$ = ND	oc: 35.17 %
Sludge 2 (Easton WWTP)		$K_{d, sludge\ 2}$ = ND $K_{oc, sludge\ 2}$ = ND Log $K_{f, sludge\ 2}$ = ND	oc: 36.09 % Adsorption of cilastatin by activated sludge solids was less than 10% at all practical solid: solution ratios. Product of solid: solution ratio and the adsorption distribution coefficient (Kd) for each of the ASS for each of the tested ratios was below 0.1. Therefore, no further testing was conducted.
Ready Biodegradability Test	OECD 301B	Average cumulative percent biodegradation = 27.7%; Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems, 100d. System 1 = *Brandywine Creek* System 2 = *Choptank River*	OECD 308	*Brandywine/Choptank* DT50, water = 2.5/2.8d DT50, sediment = ND DT50, whole system = 2.5/2.8d Corrected to 12 ℃:	DT50 values were calculated with SFO models. CIL half-lives for sediment were considered unreliable. A single major transformation product peak (>10% of applied 14C) was observed with a retention time of

		DT50, water = 5.4/6.0d DT50, sediment = ND DT50, whole system = 5.4/6.0d CO_2 (d100) = 68.2 / 94.0% NER_{total} (d100) = 14.5% / 6.6% $NER_{type\ 1}$ = ND % shifting to sediment >10% 3 transformation products whereof 1 (TP3) at >10% and the other 2 (TP4, TP5) at >5% .	approximately 11.6 minutes (TP3). This peak accounted for a maximum of 31.1% of the ^{14}C in one of the Choptank River samples on day 7.  TP4 and TP5 were observed at approximately 12.7 and 13.3 minutes.

Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC LOEC *EC_{50}*	99 >99 >99	*mg*/L *mg*/L *mg*/L	growth rate, 72h
Algae, Growth Inhibition Test/ *A. flos-aquae*	OECD 201	NOEC LOEC EC_{50}	99 >99 >99	*mg*/L *mg*/L *mg*/L	growth rate, 72h
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC LOEC EC10 EC50	10 >10 >10	*mg*/L *mg*/L *mg*/L	21d exposure. No effect at any endpoint. Highest concentration 10 mg/L.

			>10	*mg*/L	
Fish, *ELS / Fathead minnow (Pimephales promelas)*	OECD *210*	NOEC LOEC EC10	9.9 >9.9 >9.9	mg/L mg/L mg/L	5d pre-hatch + 28d post-hatch exposure. No effect at any endpoint. Highest concentration 10 mg/L (measured 9.9 mg/L).
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC LOEC EC50	1000 >1000 >1000	mg/L mg/L mg/L	total respiration Tested at 10, 100 and 1000 mg/L.
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD *218*	NOEC NOECoc10 LOEC EC50	347 2669 >347 >347	mg/kg_{dw} mg/kg_{dw} mg/kg_{dw} mg/kg_{dw}	28d exposure. OC: 1.3% No effect at any endpoint. Highest concentration 1000 mg/kg (measured 347 mg/kg).
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	10 ug/L	100 000 ug/L	1×10^{-4}		No risk
Surface water	10 ug/L	990 ug/L	0.01		No risk
Groundwater	2.5 ug/L	99 ug/L	0.025		No risk
Sediment	0.23 mg/kg	26.69 mg/kg	0.0087		No risk. The PEC for sediment was calculated using the highest soil Koc

				value for cilastatin of 198 L/kg.

2.3.6. Discussion on non-clinical aspects

No new non-clinical studies have been submitted for this procedure and this is acceptable.

The previously assessed non-clinical dossier for REL (Recarbrio) was based on general repeat-dose toxicity studies that, at the start of studies, had rats as young as approximately 6-7 weeks of age and the monkeys were approximately 1-3 months of age and would be considered developmentally similar to adolescent age. Renal excretion is the major route of elimination of REL and the main target organ for REL was the kidneys in rats and monkeys.

There were generally no differences in the repeat-dose toxicity assessment when comparing REL and IMI/REL exposures. It can be noted that IMI monotherapy has also been associated with kidney toxicity, however, when IMI is combined with CIL, CIL seems to protect against the renal toxicity induced by IMI.

REL induced CNS findings in rats (1-month and 3-month studies) manifested at doses achieving very high C_{max} concentrations but had also large safety margins (>100-fold the highest adult or paediatric C_{max} at the RHD). Like other beta-lactam antibiotics, IMI has seizurogenic potential identified in nonclinical and clinical studies at high C_{max} concentrations.

Assessment of paediatric data on non-clinical aspects

In the juvenile toxicity studies (JAV) in rat, there was no REL-related toxicity. The systemic exposure marginal between adult human and the juvenile rats administered the highest dose 450 mg/kg/day was 6x (based on $AUC_{0\text{-}24hr}$) and 78x (based on C_{max}). The safety margins to paediatric patients (clinical $AUC_{0\text{-}24hr}$ of 545 h*µM and total C_{max} of 59.9 µM based on Paediatric Population PK Model-Predicted Steady State PK Parameter Estimates for REL) were 2.5x (AUC) and 22.4x (C_{max}) for PNW4 rats and 4.3x (AUC) and 65x (C_{max}) for PNW9 rats.

Environmental risk assessments

The ERA's provided for REL and CIL are in line with 2024 CHMP ERA GL and do not identify any environmental risks. The IMI ERA is not in line with 2024 CHMP ERA GL and needs to be modified with regard to a tailored assessment for antibiotics. Based on the existing data and using the unrefined default Phase I PECsw of 10 ug/L, and unless appropriate Fpen refinement is applied, a preliminary (see ERA summary table for imipenem in section 8.5) assessment *indicate* environmental risks in STP, surface water and groundwater. A commitment has been provided to submit an updated ERA within 2 years with missing data (an OECD TG201 study for cyanobacteria, it is also noted that the future ERA must not contain any consumption-based Fpen derived PEC values and new PEC and RQ values need to be calculated). Until the final ERA has been assessed and approved, the IMI ERA status remains officially unclear.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical dossier conclusions

The MAH has discussed previously submitted non-clinical data in the context of this procedure and no new toxicological concerns have been identified.

ERA conclusions

Considering the above ERA information, REL and CIL are not expected to pose a risk to the environment. No final conclusion on the environmental risk of IMI can be made at this stage and a commitment has been provided to submit an updated ERA in the future (within 2 years after end of procedure).

Overall conclusions

There are no non-clinical concerns that would affect approval.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Tabular overview of clinical studies

<table>
<tr><th>Study Number (Status) [CTD Location]</th><th>Design Duration Indication</th><th>Number of Participants by Intervention Group</th><th>Study Population</th></tr>
<tr>
<td>MK-7655A-021 (completed)</td>
<td>Phase 2/3, randomized, active-controlled, parallel-group, multisite, open-label study

Study Intervention Duration: 5 to 14 days
Male and female paediatric participants with confirmed or suspected G-bacterial infection</td>
<td>By Age Cohort:
<table>
<tr><th>Age Cohort
Age Range</th><th>IMI/REL:
Randomized/
Treated/
Completed Study
Dosing Regimen[a]</th><th>Active Control:
Randomized/
Treated/
Completed Study
Dosing Regimen[b]</th></tr>
<tr><td>1
12 to <18 yrs</td><td>10/10/10
500/250 mg q6h</td><td>2/2/2</td></tr>
<tr><td>2
6 to <12 yrs</td><td>31/31/31
15/7.5 mg/kg q6h</td><td>11/11/11</td></tr>
<tr><td>3
2 to <6 yrs</td><td>22/21/21
15/7.5 mg/kg q6h</td><td>8/8/8</td></tr>
<tr><td>4
3 mos to <2 yrs</td><td>15/15/15
15/7.5 mg/kg q6h</td><td>5/4/4</td></tr>
<tr><td>5
birth to <3 mos</td><td>8/8/7
15/7.5 mg/kg q8h</td><td>3/3/3</td></tr>
</table></td>
<td>APaT Population:
Sex:
IMI/REL:
49.4% M/50.6% F
Active Control:
53.6% M/46.4% F

Infection Type:
IMI/REL:HABP/VABP 5.9%, cIAI 45.9%, cUTI 48.2%
Active Control:
HABP/VABP 3.6%, cIAI 50.0%, cUTI 46.4%</td>
</tr>
<tr>
<td>MK-7655A-020 (completed)
21 sites (8 countries)</td>
<td>Phase 1b, open-label, single-dose study

Study Intervention Duration: Single dose of IMI/REL
Male and female paediatric participants with confirmed or suspected G-bacterial infection</td>
<td>All randomized participants population
Overall:
47 allocated / 46 treated / 46 completed study / 46 completed study intervention / 1 discontinued study / 0 discontinued study intervention
By Age Cohort:
<table>
<tr><th>Age Cohort
Age Range</th><th>Initial IMI/REL Dosing Regimen</th><th>Modified IMI/REL Dosing Regimen Based on Interim Reviews</th><th>Allocated/
Treated/
Completed Study</th></tr>
<tr><td>1
12 to <18 yrs</td><td>15/7.5 mg/kg over 30 min (n=4)</td><td>500/250 mg over 30 min
(n=3)</td><td>7/7/7</td></tr>
</table></td>
<td>All Randomized Population:
Overall:
Sex: 40.4% M/59.6% F</td>
</tr>
</table>

Study Number (Status) [CTD Location]	Design Duration Indication	Number of Participants by Intervention Group				Study Population
		2 6 to <12 yrs	15/7.5 mg/kg over 30 min (n=3)	15/7.5 mg/kg over 60 min (n=3)	6/6/6	
		3 2 to <6 yrs	15/7.5 mg/kg over 30 min (n=3)	15/7.5 mg/kg over 60 min (n=3)	6/6/6	
		4 3 mos to <2 yrs	10/5 mg/kg over 60 min (n=4)	15/7.5 mg/kg over 60 min (n=4)	8/8/8	
		5 birth to <3 mos	10/5 mg/kg over 60 min (n=10)	15/7.5 mg/kg over 60 min (n=9)	20/19/19	

%*f*T>MIC=percent time of dosing interval that unbound plasma concentrations exceed the minimum inhibitory concentration; AE=adverse event; APaT=all participants as treated; AUC=area under the plasma concentration-time curve; $AUC_{0\text{-}24hr}$=area under the plasma concentration time curve from time 0 to 24 hours; C_{eoi}=concentration at end of infusion; cIAI=complicated intra-abdominal infection; CL=clearance; C_{max}=maximum concentration; CTD=Common Technical Document; cUTI=complicated urinary tract infection; ECIs=events of clinical interest; EFU=early follow-up; EOT=end of treatment; F=female; HABP=hospital-acquired bacterial pneumonia; IMI/REL=imipenem/cilastatin/relebactam; IV=intravenous; LFU=late follow-up; M=male; MITT=modified intent-to-treat; mMITT=microbiological modified intent-to-treat; mos=months; n=number of participants; PI=Package Insert; PK=pharmacokinetic; q6h=every 6 hours; q8h=every 8 hours; REL= relebactam; SPC=Summary of Product Characteristics; VABP=ventilator-associated bacterial pneumonia; Vc=central volume of distribution; yr(s)=year(s).

[a] IMI/REL dosage level as a 60 min IV infusion.

[b] Active control dosage level per authorized PI, SPC, or international treatment guidelines.

2.5. Pharmacokinetics

IMI/REL is approved for use in adults ≥18 years of age for multiple indications, including cUTI, cIAI, and HABP/VABP, by global health authorities, including the US, EU, and Japan. The approved adult dose of IMI/REL is 1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) administered by IV infusion in patients with normal renal function, dose adjustments are recommended in patients with renal impairment categories. This supplemental marketing application provides data to support the extension of the use of IMI/REL for the treatment of suspected or confirmed gram-negative bacterial infections in paediatric populations from birth to <18 years of age. The clinical development program for the paediatric population includes 2 clinical studies: a single-dose Phase 1 study (P020) and a multiple dose Phase 2/3 study (P021). This program was designed to provide adequate PK data as a basis for extrapolation of efficacy, and to an extent safety.

Cilastatin protects imipenem from degradation by the enzyme dihydropeptidase in human kidneys, and where any clinically meaningful change in cilastatin PK would also manifest as a clinically relevant difference in imipenem PK. Therefore, as described in the original adult application, a popPK model for cilastatin was not developed.

IMI/REL is approved for use in adults ≥18 years of age for multiple indications, including cUTI, cIAI, and HABP/VABP, by global health authorities, including the US, EU, and Japan. The approved adult dose of IMI/REL is 1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) administered by IV infusion in patients with normal renal function, dose adjustments are recommended in patients with renal impairment categories. This supplemental marketing application provides data to support the extension of the use of IMI/REL for the treatment of suspected or confirmed gram-negative bacterial infections in paediatric populations from birth to <18 years of age. The clinical development program for the paediatric population includes 2 clinical studies: a single-dose Phase 1 study (P020) and a multiple dose Phase 2/3 study (P021). This program was designed to provide adequate PK data as a basis for extrapolation of efficacy, and to an extent safety.

Cilastatin protects imipenem from degradation by the enzyme dihydropeptidase in human kidneys, and where any clinically meaningful change in cilastatin PK would also manifest as a clinically relevant difference in imipenem PK. Therefore, as described in the original adult application, a popPK model for cilastatin was not developed.

2.5.1. Evaluation and qualification of models

Several popPK models have been developed throughout the clinical development of IMI/REL, with separate models for each active substance (imipenem and REL). These models integrated data from multiple clinical studies and supported global registrations for adults in the setting of cUTI/cIAI and HABP/VABP indications.

In this application, the company has submitted 2 popPK analyses:

1. Preliminary paediatric population pharmacokinetic and probability of target attainment analyses in support of paediatric clinical studies P020 and P021.
2. Population Pharmacokinetic, Exposure-Response and Probability of Target Attainment Analysis of Imipenem and Relebactam in Combined Phase 1 and Phase 2/3 Studies in the Paediatric Population

The 2nd report, using all the paediatric data from both paediatric studies, was used to support extrapolation of efficacy and safety from adults to children. This model is described below.

Population PK *(Population Pharmacokinetic, Exposure-Response and Probability of Target Attainment Analysis of Imipenem and Relebactam in Combined Phase 1 and Phase 2/3 Studies in the Paediatric Population)*

Objectives

- To characterise the pharmacokinetics (PK) of imipenem and relebactam (REL) in paediatric participants (birth to <18 years of age
- To compare adult exposure distributions with paediatric exposure distributions to support paediatric dosing recommendations
- To simulate probability of target attainment to further support the proposed posology

Dataset

Plasma concentrations from 131 paediatric participants across Study P020 (N=46) and Study P021 (N=85) were available for the population PK analysis. The 131 participants provided 1034 total plasma observations, 517 each for imipenem and REL (184 from Study P020 and 333 from Study P021). Greater than 70% (377 for imipenem and 383 for REL) of observations were above the limit of quantitation for both imipenem and REL. Of the below the lower limit of quantification (BLQ) observations, a majority (90% and 94% for imipenem and REL respectively) were pre-dose observations on Day 1 and less than 3% of post dose observations for both drugs were BLQ. Therefore, for the development of imipenem and REL PPK models, the percentage of relevant samples for BLQ was considered to be low and excluded from modelling analysis. After having accounted for the data exclusions discussed above, plasma concentrations versus time since the last dose are presented in [Figure 1 and Figure 2] for imipenem and REL, respectively. A summary of studied participants by age cohorts and body weight groups is displayed in [Table 8 and Table 9]. Study P020 included more participants in the youngest age cohorts than Study P021, and consequently, Study P020 also included more participants in the lower weight groups than Study P021. The youngest participant was included in Study P020 and was 2 days old. Participant weight ranged from 2.52 to 73.0 kg.

Plasma concentrations of imipenem, cilastatin, and REL were determined using a validated high-performance liquid chromatographic tandem mass spectrometric method.

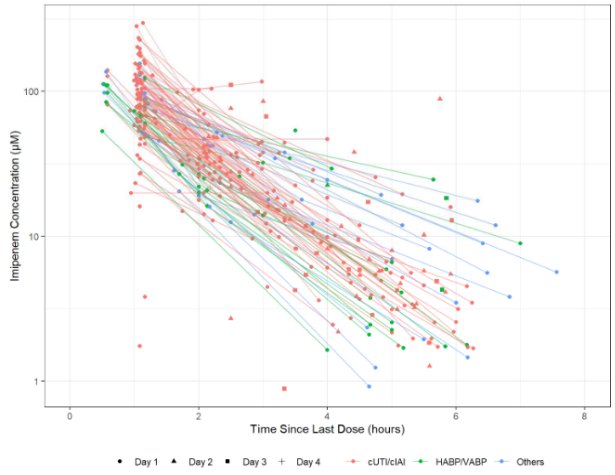
P020: A Phase 1b, Open-label, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of MK-7655A in Paediatric Subjects From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Infections.
P021: A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Paediatric Participants From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection

Table 7 Summary of PK Observations and Exclusions by Study

Study	Analyte	Participants N	Observations n	Available for PK Analysis, n (%)	Pre-first Dose BLQ, n (%)	Post-first Dose BLQ, n (%)	Day-1 Predose Non-zero Concentration, n (%)	Outlier Concentration, n (%)	EOI Concentration <LOQ, n (%)
P020	Imipenem	46	184	134 (72.8)	44 (23.9)	3 (1.63)	2 (1.09)	1 (0.543)	0 (0)
P020	REL	46	184	137 (74.5)	45 (24.5)	0 (0)	1 (0.543)	1 (0.543)	0 (0)
P021	Imipenem	85	333	237 (71.2)	82 (24.6)	10 (3)	3 (0.901)	0 (0)	1 (0.3)
P021	REL	85	333	240 (72.1)	81 (24.3)	7 (2.1)	4 (1.2)	0 (0)	1 (0.3)

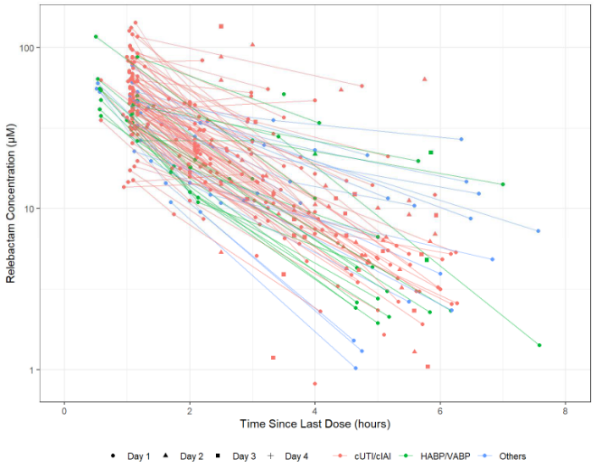
Source: MK7655A-pediatric-p20-p21-eda-v8.html
Abbreviations: BLQ=below the limit of quantification; EOI=end of infusion; LOQ=limit of quantification; n=number of observations, N=number of participants; PK=pharmacokinetic; REL=relebactam

Figure 1 Imipenem Plasma Concentrations Versus Time Since Last Dose by Infection Type



Source: MK7655A-pediatric-p20-p21-eda-v8.html
Notes: the symbols represent concentration at the indicated time for individual participants (different symbols are used for different days). One extreme outlier (caused by wrong sample collection) excluded from the model was also excluded from the PK profiles presented in this figure.
Abbreviations: cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; PK=pharmacokinetic(s)

Figure 2 REL Plasma Concentrations Versus Time Since Last Dose by Infection Type



Source: MK7655A-pediatric-p20-p21-eda-v8.html
Notes: The symbols represent concentration at the indicated time for individual participants (different symbols are used for different days). One extreme outlier (caused by wrong sample collection) excluded from the model was also excluded from the PK profiles presented in this figure.
Abbreviations: cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; PK=pharmacokinetic(s); REL=relebactam

Table 8 Summary of Pediatric Study Participants by Cohort and Weight Categories

	P020 (N=46)	P021 (N=85)	Overall (N=131)
Cohort			
Cohort 1 ≥12 years to <18 years, N (%)	7 (15.2)	10 (11.8)	17 (13.0)
Cohort 2 ≥6 years to <12 years, N (%)	6 (13.0)	31 (36.5)	37 (28.2)
Cohort 3 ≥2 years to <6 years, N (%)	6 (13.0)	21 (24.7)	27 (20.6)
Cohort 4 ≥3 months to <2 years, N (%)	8 (17.4)	15 (17.6)	23 (17.6)
Cohort 5 Birth to <3 months, N (%)	19 (41.3)	8 (9.4)	27 (20.6)
Weight group			
WT ≥70 kg, n (%)	0 (0)	1 (1.2)	1 (0.8)
WT [60 to <70 kg), N (%)	0 (0)	2 (2.4)	2 (1.5)
WT [50 to <60 kg), N (%)	4 (8.7)	5 (5.9)	9 (6.9)
WT [40 to <50 kg), N (%)	5 (10.9)	7 (8.2)	12 (9.2)
WT [30 to <40 kg), N (%)	2 (4.3)	12 (14.1)	14 (10.7)
WT [25 to <30 kg), N (%)	1 (2.2)	1 (1.2)	2 (1.5)
WT [20 to <25 kg), N (%)	0 (0)	14 (16.5)	14 (10.7)
WT [15 to <20 kg), N (%)	4 (8.7)	12 (14.1)	16 (12.2)
WT [10 to <15 kg), N (%)	5 (10.9)	12 (14.1)	17 (13.0)
WT [5 to <10 kg), N (%)	10 (21.7)	13 (15.3)	23 (17.6)
WT <5 kg, N (%)	15 (32.6)	6 (7.1)	21 (16.0)
WT <2 kg, N (%)	0 (0)	0 (0)	0 (0)

Source: MK7655A-pediatric-p20-p21-eda-v8.html
Abbreviations: N=number of participants; WT=baseline body weight

Table 9 Summary of Pediatric Participants by Age Cohort Categories

	P020 (N=46)	P021 (N=85)	Overall (N=131)
Cohort			
Cohort 1 ≥12 years to <18 years, N (%)	7 (15.2)	10 (11.8)	17 (13.0)
Cohort 2 ≥6 years to <12 years, N (%)	6 (13.0)	31 (36.5)	37 (28.2)
Cohort 3 ≥2 years to <6 years, N (%)	6 (13.0)	21 (24.7)	27 (20.6)
Cohort 4 ≥3 months to <2 years, N (%)	8 (17.4)	15 (17.6)	23 (17.6)
Cohort 5 ≥2 months to <3 months, N (%)	3 (6.5)	4 (4.7)	7 (5.3)
Cohort 5 ≥1 month to <2 months, N (%)	3 (6.5)	3 (3.5)	6 (4.6)
Cohort 5 Birth to <1 month, N (%)	13 (28.3)	1 (1.2)	14 (10.7)
Abbreviations: N=number of participants ; values in the parenthetical represents the %			

Source: [Ref. 5.3.5.3: 08PWP8]

The CHMP noted that the dataset includes both single dose and multiple dose data from 2 paediatric studies. 27 subjects from birth to less than 3 months are included in the dataset and thus an indication down to birth should be possible. The MAH has provided a table showing that 14 of the subjects were below 1 month of age (Table 9). Based on the observed data figure, it can be seen that exposure of IMI and REL for cUTI/cIAI, HABP/VABP and other infections subjects are largely overlapping. The majority of paediatric data are from cUTI/cIAI subjects. Less than 3% of post dose observations for both drugs were BLQ and excluded from modelling analysis. The CHMP considered this to be acceptable since the percentage BLQ of the post dose observations were low.

Methods

The population PK analysis was performed using the nonlinear mixed-effects modeling approach. The nonlinear mixed-effects modelling software (NONMEM® v 7.5.1) was used.

For both drugs, popPK models were developed separately using only the paediatric data. The previously established 2-compartmental PPK models in adults were used as a starting point for the development of paediatric models. As part of structural model development, allometric scaling (AS) of body weight for CL and intercompartmental CL (Q), central volume of distribution (Vc), and peripheral volume of distribution (Vp) was included using fixed standard exponents of 1 for Vc and Vp, and 0.75 for CL and Q. Estimation of these exponents was examined as well. Renal maturation function (RMF) was assessed as part of the structural model development. For RMF, it was described using postmenstrual age (PMA) as proposed by Rhodin et al.

The standard stepwise covariate analysis was not conducted. After incorporating fixed AS for body weight, renal maturation effects, and fixed eGFR effects on CL in the models of imipenem and REL, no additional trends were identified.

The CHMP noted that the final models include fixed allometric scaling. Imipenem and relebactam are mainly excreted by the kidneys. The MAH has considered this by including a maturation function from literature. Including allometric scaling and considering maturation was therefore supported by the CHMP.

Final Imipenem popPK Model

Parameter estimates for the final imipenem PPK model are provided in [Table 10] along with the bootstrap parameter estimates. All parameters were estimated with good precision, with 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.

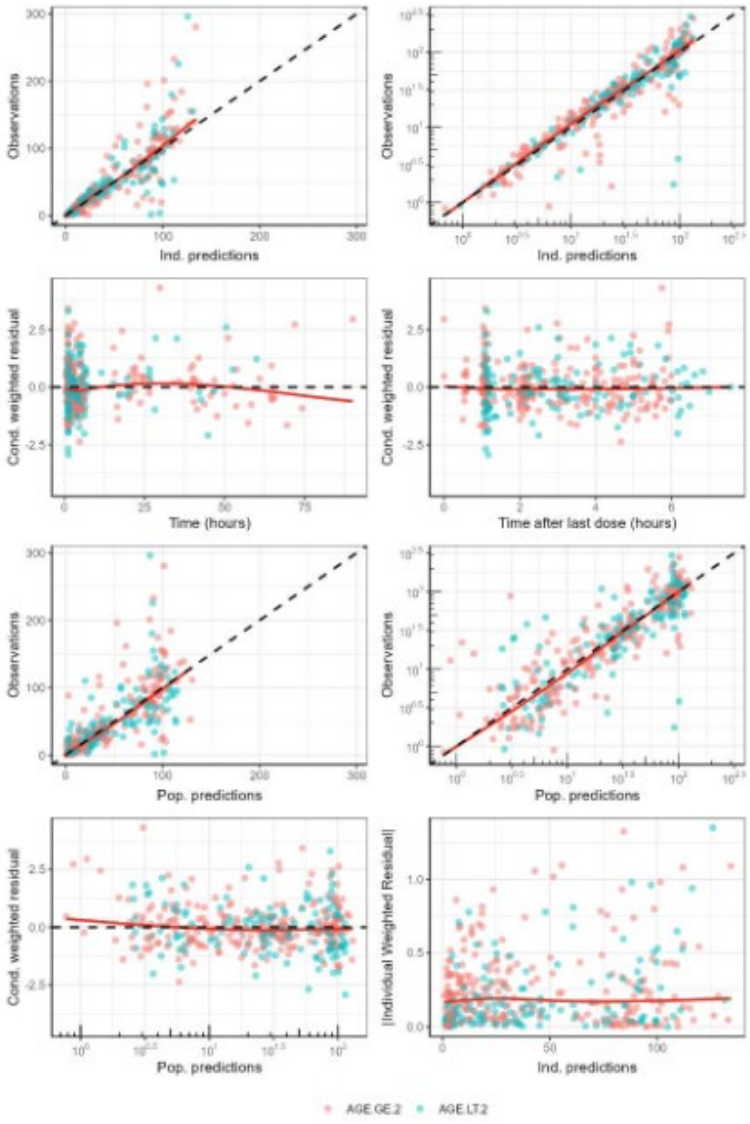
Model evaluation using standard GOF diagnostic plots [Figure 3] and simulation-based pcVPCs indicated that the model adequately characterised the central tendency and variability of the observed imipenem concentration-time data overall and across all age and weight categories (Figure 4] and Figure 5] for pcVPC stratified by age cohorts and weight categories, respectively.

Table 10 Final Imipenem Model Parameter Estimates (Model 1509)

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%

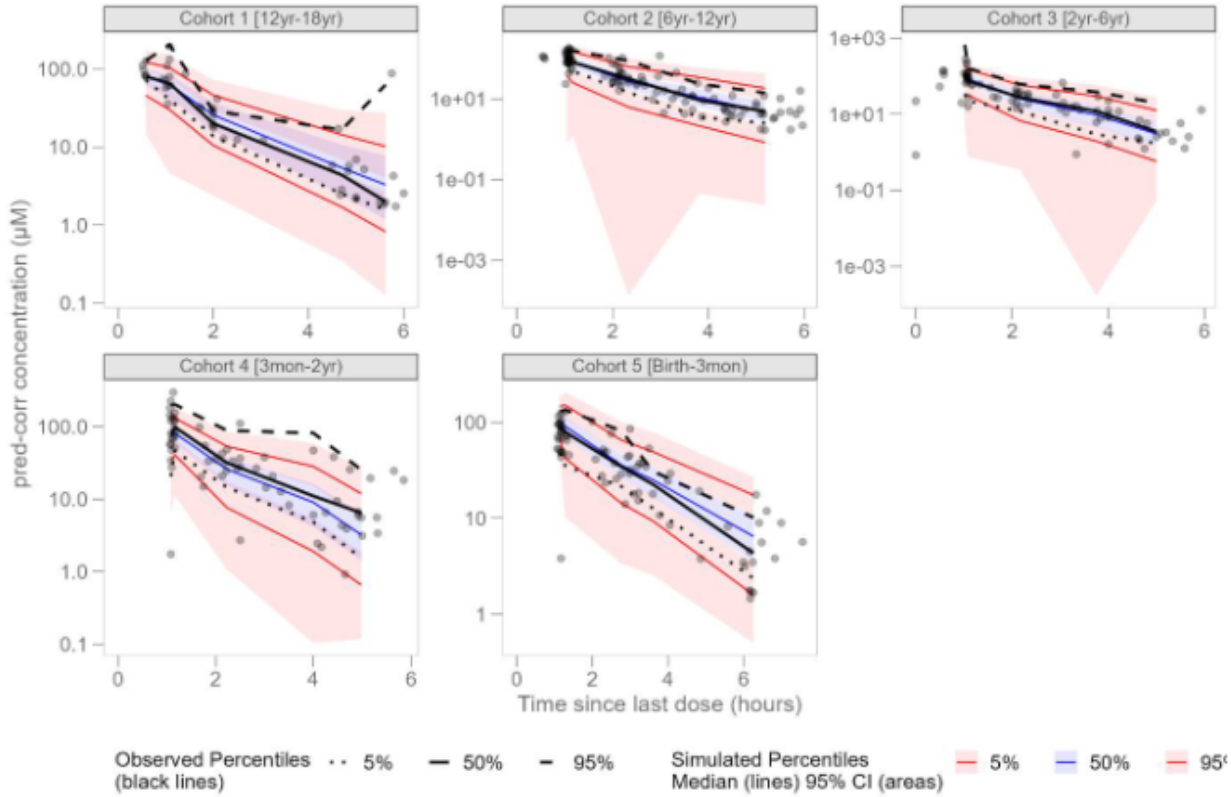
Source: run1509_param-gof-vpc-cov-poppk-Ped-imipenem-v9.html
Notes: RSE% is derived from the following equation: (standard error/mean) × 100; CV% is derived from the following equation: 100 × sqrt(exp(x) - 1); bootstrap is based on n=1000 dataset replicates.
Abbreviations: AS=allometric scaling; CI=confidence 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; TM_{50}=maturation half time; Vc=central volume of distribution; Vp=peripheral volume of distribution; WT=baseline body weight

Figure 3 Log-Log and Linear Standard Diagnostics Plots from the Final Imipenem Model Colored by Age Categories (Model 1509) – Observations Versus Individual and Population Predictions; CWRES Versus Time, Time After Last Dose and Population Predictions; and IWRES Versus Individual Predictions



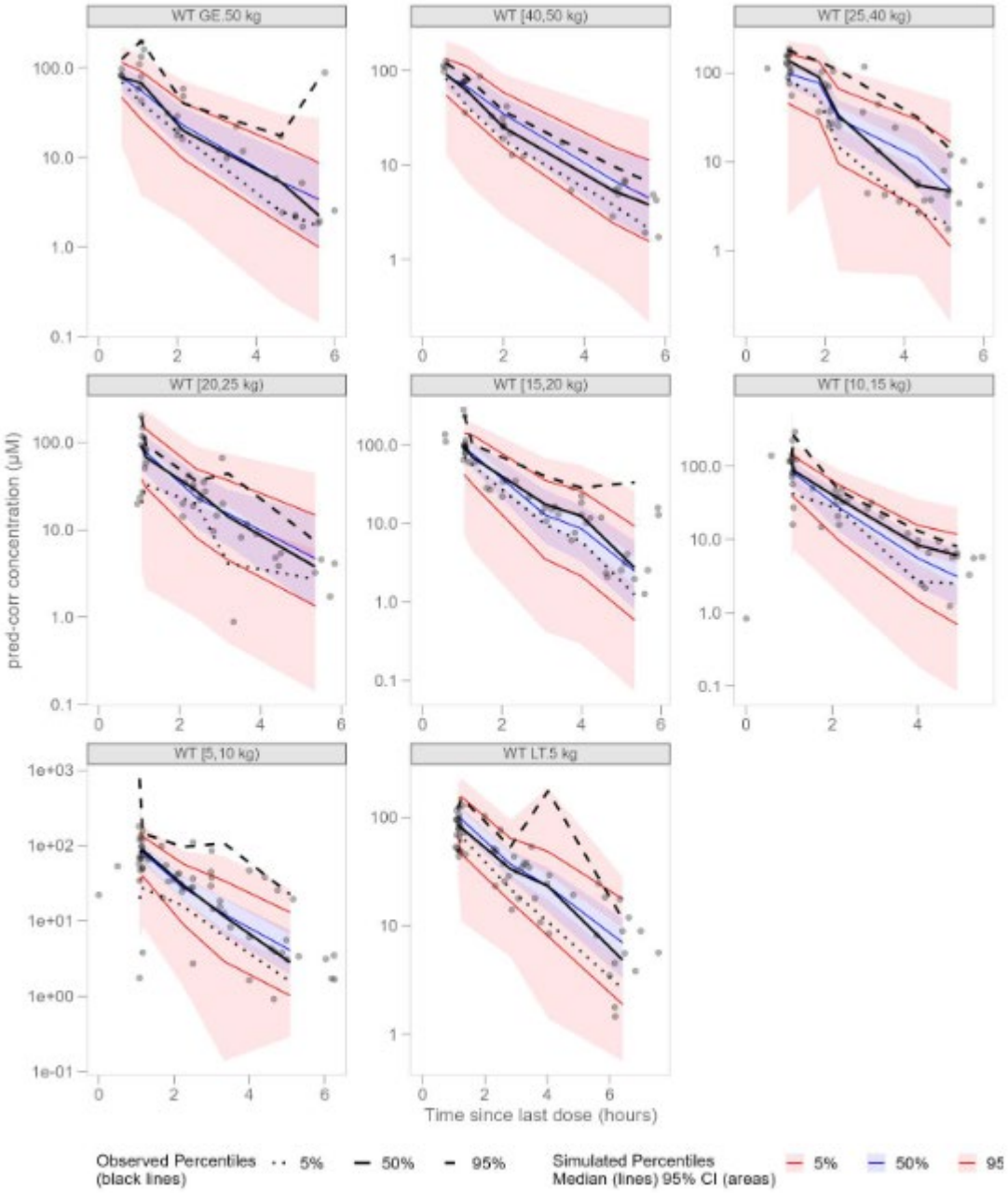
run1509_param-gof-vpc-cov-poppk-Ped-imipenem-v9.html
Notes: Circles represent individual observations; the red solid line represent a loess fit.
Abbreviations: AGE.GE.2=age ≥2; AGE.LT.2=age <2; CWRES=conditional weighted residuals; Ind=individual; IWRES=individual weighted residuals; loess=locally estimated scatterplot smoothing; pop=population

Figure 4 pcVPC from the Final Imipenem Model Stratified by Age Categories (Semi-Logarithmic Scale)



run1509_param-gof-vpc-cov-poppk-Ped-imipenem-v9.html
Notes: Gray circles represent individual pred-corr observations.
Abbreviations: CI=confidence interval; mon=months; pcVPC=prediction-corrected visual predictive check; pred-corr=prediction-corrected

Figure 5 pcVPC from the Final Imipenem Model Stratified by Weight Categories (Semi-Logarithmic Scale)



run1509_param-gof-vpc-cov-poppk-Ped-imipenem-v9.html
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

The CHMP noted that the adult 2-compartment model was used as a starting point. The RSE for the final model are considered reasonable, and the GOF plots do not indicate any major misspecification. pcVPC were provided both stratified on age and on body weight. Generally, the VPCs support that the model can adequately describe the data. For some of the VPCs, several observations are not within the plotted bins. The simulated 5th percentile also appears to fall systematically slightly below the observed

5th percentile. Simulating slightly lower exposure are considered conservate with regards to efficacy and probability of target attainment and are not considered a big concern here.

The CHMP was of the view that the GOF and pcVPCs indicate that the models are fit for purpose.

Final relebactam popPK model

Parameter estimates for the final REL popPK model are provided in [Table 11] along with the bootstrap parameter estimates. All parameters were estimated with good precision, with 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.

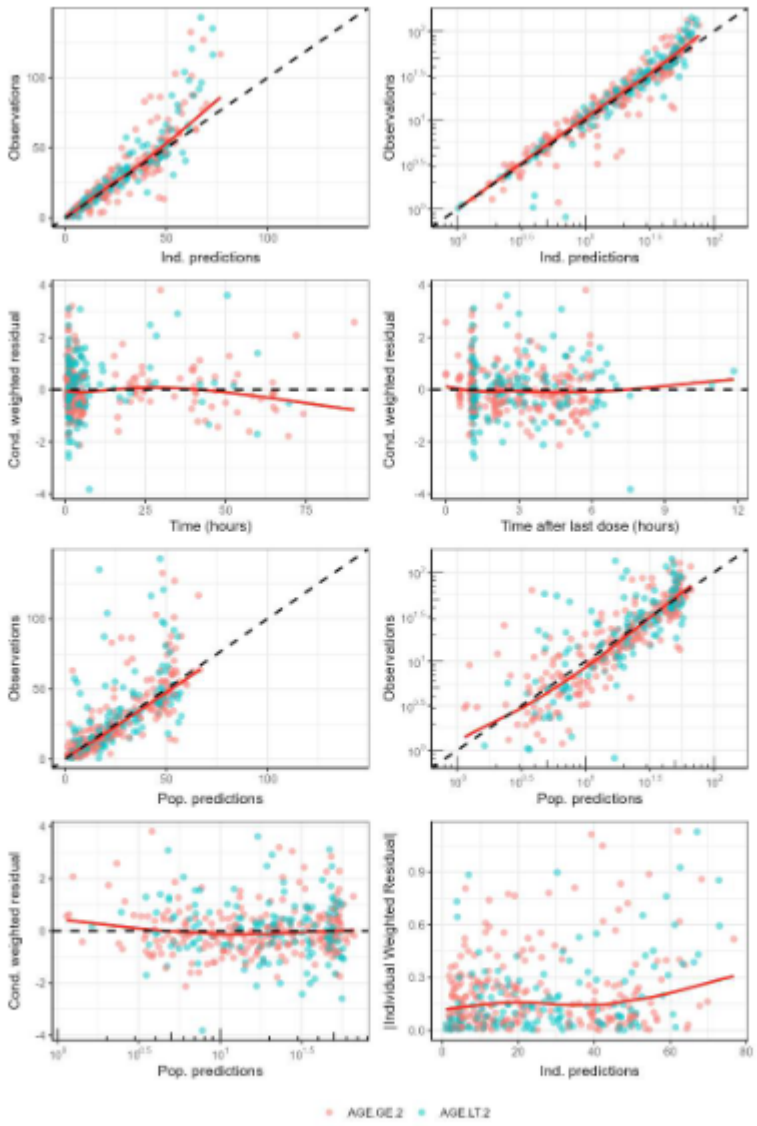
Model evaluation using standard GOF diagnostic plots] and [Figure 6] for GOF and simulation-based pcVPCs indicated that the model adequately characterised the central tendency and variability of the observed REL concentration-time data overall and across all age and weight categories ([Figure 7] and [Figure 8] for pcVPC stratified by age cohorts and weight categories, respectively.

Table 11 Final REL Model Parameter Estimates (Model 2509)

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%

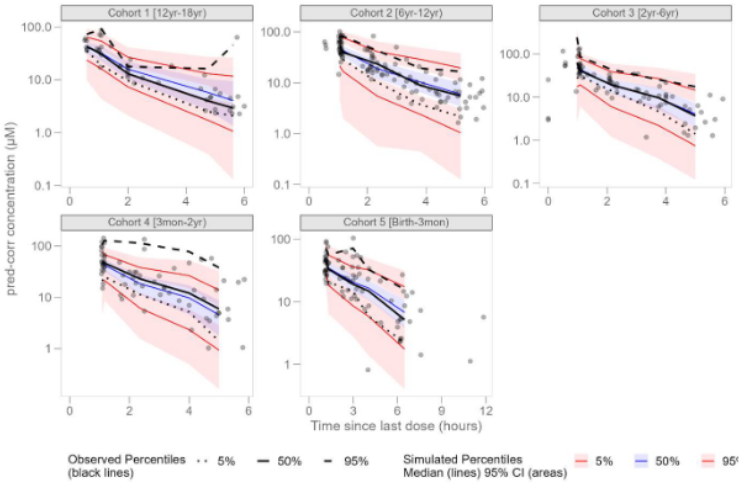
Source: run2509_param-gof-vpc-cov-poppk-Ped-relebactam-v9.html
Notes: RSE% is derived from the following equation: (standard error/mean) × 100; CV% is derived from the following equation: 100 × sqrt(exp(x) - 1); bootstrap is based on n=1000 dataset replicates.
Abbreviations: AS=allometric scaling; CI=confidence interval; CL=clearance; CV=coefficient of variation; IIV=interindividual variability; n/a=not available; PMA=postmenstrual age; Q=intercompartmental clearance; RSE=relative standard error; sqrt=square root; TM_{50}=maturation half time; Vc=central volume of distribution; Vp=peripheral volume of distribution; WT=baseline body weight

Figure 6 Log-Log and Linear Standard Diagnostics Plots from the Final REL Model Colored by Age Categories (Model 2509) - Observations Versus Individual and Population Predictions; CWRES Versus Time, Time After Last Dose, and Population Predictions; and IWRES Versus Individual Predictions



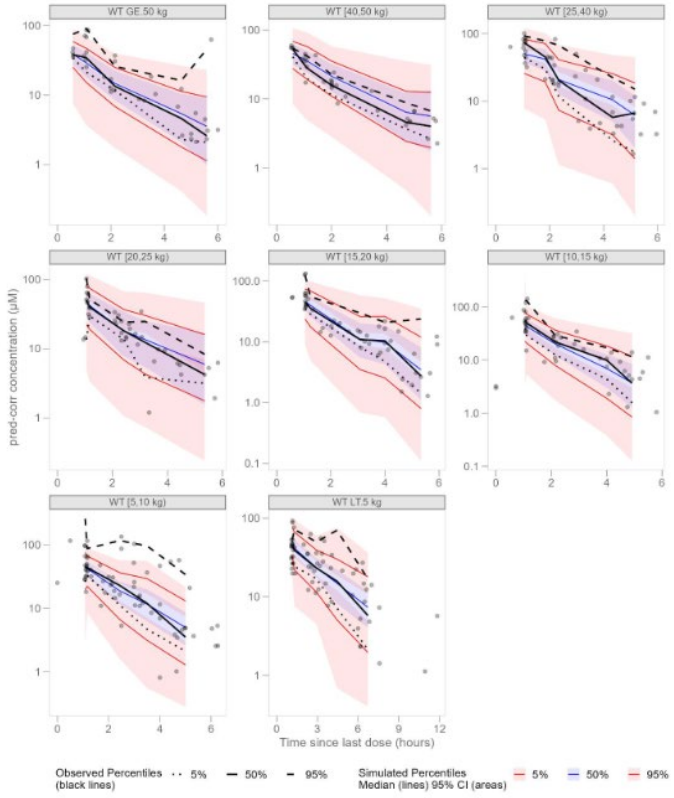
Source: run2509_param-gof-vpc-cov-poppk-Ped-relebactam-v9.html
Notes: Circles represent individual observations; the red solid line represent a loess fit.
Abbreviations: AGE.GE.2=age ≥2; AGE.LT.2= age <2; Cond=conditional; CWRES=conditional weighted residuals; Ind=individual; IWRES=individual weighted residuals; loess=locally estimated scatterplot smoothing; pop=population; REL=relebactam.

Figure 7 pcVPC from the Final REL Model Stratified by Age Categories (Semi-Logarithmic Scale)



Source: run2509_param-gof-vpc-cov-poppk-Ped-relebactam-v9.html
Notes: Gray circles represent individual pred-corr observations.
Abbreviations: CI=confidence interval; mon=months; pcVPC=prediction-corrected visual predictive check; pred-corr=prediction-corrected; REL=relebactam

Figure 8 pcVPC from the Final REL Model Stratified by Weight Categories (Semi-Logarithmic Scale)



Source: run2509_param-gof-vpc-cov-poppk-Ped-relebactam-v9.html
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; REL=relebactam; WT=baseline body weight

The CHMP noted that the adult 2-compartment model was used as a starting point. The RSE for the final model are considered reasonable, and the GOF plots do not indicate any major misspecification. pcVPC were provided both stratified on age and on body weight. Generally, the VPCs support that the

model can adequately describe the data. For some of the VPCs, several observations are not within the plotted bins. The simulated 5th percentile also appears to fall systematically slightly below the observed 5th percentile. Simulating slightly lower exposure are considered conservate with regards to efficacy and probability of target attainment and are not considered a big concern here.

The CHMP was of the view that the GOF and pcVPCs indicate that the models are fit for purpose.

Exposure in target (paediatric) population

Steady-state PK profiles were simulated for the virtual paediatric population. The extrapolation of efficacy and, to a large extent, safety, relies on exposure matching. The adult target exposures are presented in Table 12. The adult exposure from phase 2/3 was included in the figures. Given the insufficient paediatric data to identify differences in PK by infection type, a sensitivity analysis was conducted to simulate HABP/VABP paediatric patients by using fixed pneumonia effects from adult analysis.

Table 12 Descriptive Summary of Reference PK Exposures from Phase 2/3 Adult Participants (cUTI/cIAI and HABP/VABP) with Normal Renal Function (CLcr ≥90 mL/min) for Imipenem and REL Following Administration of IMI/REL Dosing Regimen Approved in Adults

Drug	Parameter	Infection Type	N	Median	GM (CV%)	25th to 75th Percentiles	10th to 90th Percentiles	5th to 95th Percentiles	Range [Min, Max]
Imipenem	$AUC_{0\text{-}24h}$ (μM×h)	cIAI/cUTI	379	445.16	456.11 (58.066)	[332.48 to 582.62]	[243.3 to 842.25]	[208.47 to 1234.2]	[103.26, 4497.7]
		HABP/VABP	156	728.41	764.27 (74.216)	[527.06 to 1024.8]	[373.31 to 1531.8]	[303.74 to 3375.6]	[149.42, 11283]
	Cmax (μM)	cIAI/cUTI	379	78.098	76.185 (60.688)	[55.454 to 104.64]	[40.288 to 143.95]	[31.378 to 197.2]	[12.656, 503.52]
		HABP/VABP	156	116.09	116 (78.09)	[83.248 to 152.76]	[53.161 to 238.05]	[44.479 to 357.85]	[11.157, 2144.8]
REL	$AUC_{0\text{-}24h}$ (μM×h)	cIAI/cUTI	258	337.21	348.96 (50.964)	[272.02 to 453.44]	[199.5 to 603.65]	[160.04 to 829.95]	[67.679, 2537.5]
		HABP/VABP	157	535.59	554.9 (57.305)	[380.04 to 747.31]	[306.12 to 976.7]	[255.57 to 1502.1]	[143.07, 4836.2]
	Cmax (μM)	cIAI/cUTI	258	46.133	45.484 (49.201)	[33.831 to 59.721]	[26.242 to 83.614]	[20.955 to 93.472]	[8.6405, 316.9]
		HABP/VABP	157	58.496	62.464 (49.899)	[46.527 to 80.485]	[37.076 to 107.04]	[29.665 to 148.1]	[18.999, 356.86]

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; CV coefficient of variation; GM geometric mean; HABP/VABP hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI/REL imipenem/cilastatin/relebactam combination; Max maximum; Min minimum; N number of participants; PK pharmacokinetic; REL relebactam; The descriptive summary of PK exposures from the Phase 2/3 adult participants with normal renal function (CLcr ≥90 mL/min) is derived from individual post-hoc parameter estimates from Studies P003 (cUTI), P004 (cIAI), P013 (cUTI,cIAI & HABP/VABP), and P014 (HABP/VABP) using final adult popPK model(s).

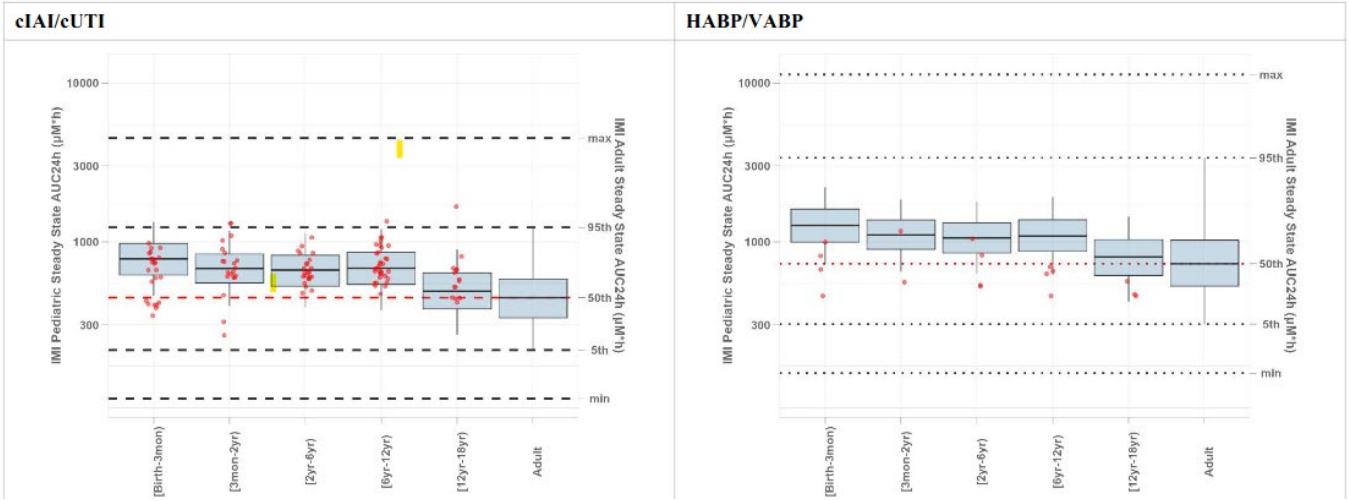
Source: [Ref. 5.3.5.3: 08PWP8: Adapted from Table 69]

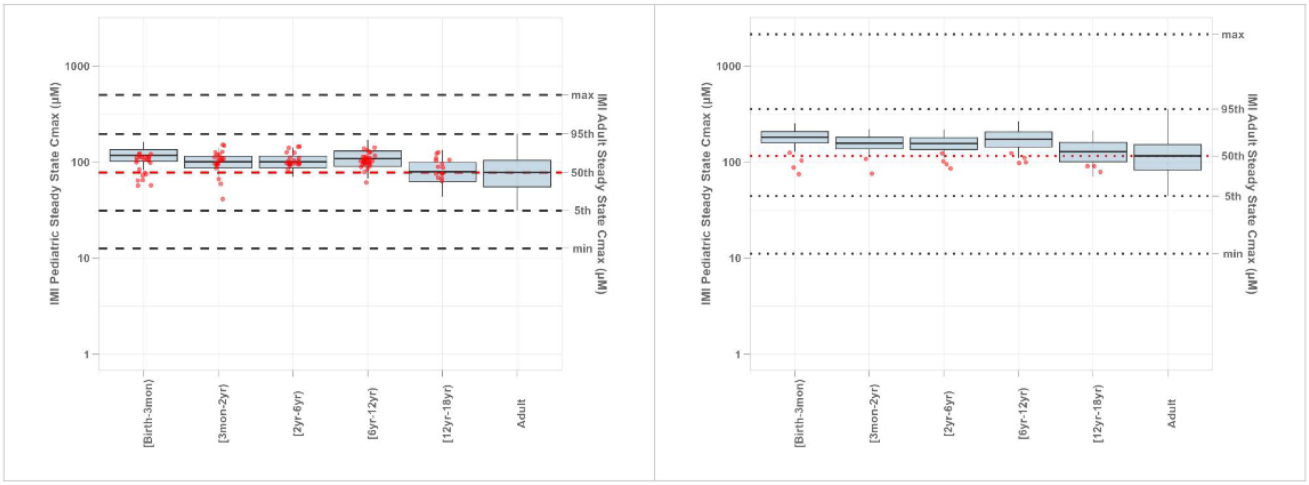
Table 13 Population pharmacokinetic model based geometric mean (% geometric co-efficient of variation) steady-state plasma pharmacokinetic parameters following administration of the recommended dosing regimens in HABP/VABP, cUTI or cIAI paediatric patients (birth to <18 years) with normal renal function

Body Weight	Age	Imipenem				Relebactam			
		$AUC_{0\text{-}24hr}$ (µM.hr)	C_{max} (µM)	$t_{1/2}$ (hr)	CL (L/hr/kg)	$AUC_{0\text{-}24hr}$ (µM.hr)	C_{max} (µM)	$t_{1/2}$ (hr)	CL (L/hr/kg)
≥30 kg	<18 years (N=38)	662 (38.8)	116 (23.3)	1.67 (26.6)	0.235 (25.9)	428 (45)	61.1 (27.2)	1.85 (26.3)	0.156 (28.7)
<30 kg	≥3 months and <18 years (N=66)	715 (27.4)	104 (15.1)	1.37 (19.6)	0.28 (24.2)	474 (49.9)	57.2 (23.2)	1.57 (29.2)	0.182 (32.8)
<30 kg	Birth to <3 months (N=27)	749 (21.6)	111 (13.2)	1.55 (20.3)	0.201 (20.1)	545 (44.5)	59.9 (21.6)	2.09 (39.4)	0.119 (35.3)

$AUC_{0\text{-}24hr}$=area under the concentration time curve from 0 to 24 hours; C_{max}=maximum concentration; $t_{1/2}$=elimination half-life; CL=body weight normalised plasma clearance

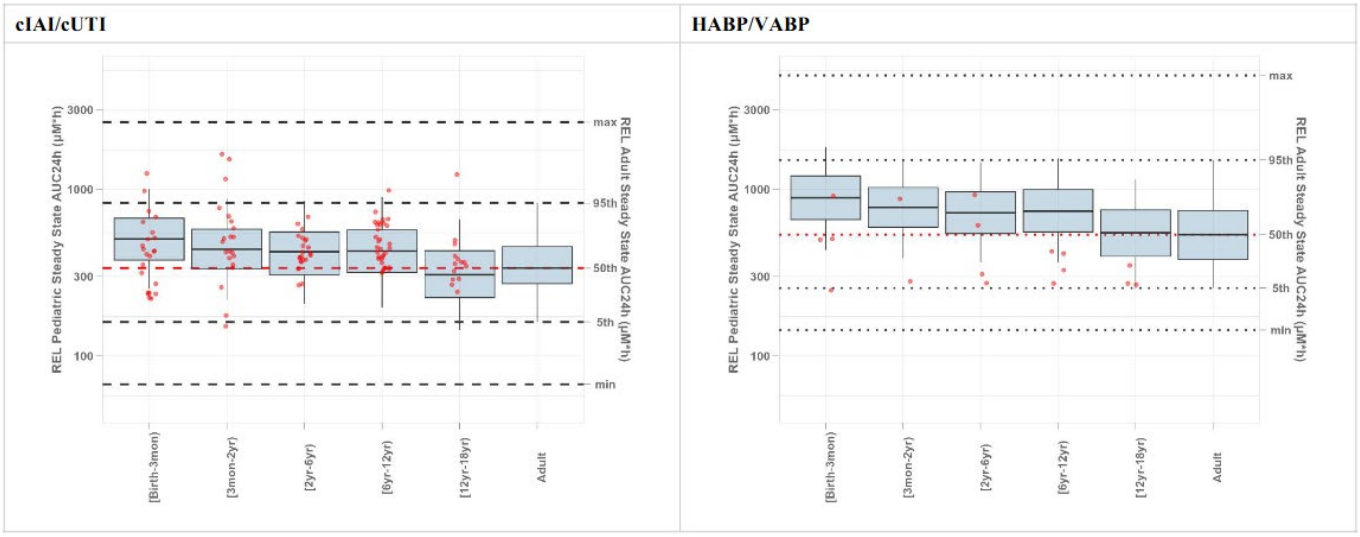
Figure 9 Comparison of Imipenem Final Pediatric PPK Model-Predicted Steady-State Exposures (AUCo-24h [Top] and Cmax [Bottom]) in Virtual Pediatric Population Following Recommended IMI/REL Dosing Regimen Administration and in Studied Pediatric Patients and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI/REL Dosing Regimen Administration Stratified by Age Categories

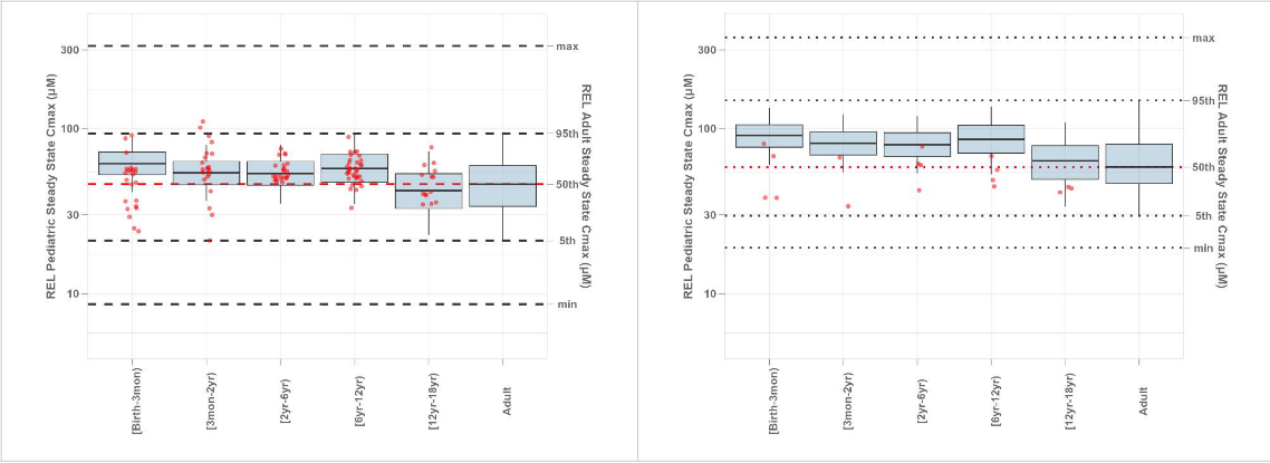




Source: simulations-virtual-poppk-imi-rel-peds-vs-adult-ref-normal-renal-v10-pdose-30kg-q8hc5.html
Notes: Boxplots represent the simulated pediatric exposures; the blue area represents the interquartile interval, the thick black line corresponds to the median; and the lower and upper whiskers extend 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; Cmax=maximum concentration; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI=imipenem/cilastatin; IMI/REL=imipenem/cilastatin/relebactam combination; max=maximum; min=minimum; PPK=population pharmacokinetics

Figure 10 Comparison of REL Final Pediatric PPK Model-Predicted Steady-State Exposures AUCo-24h [Top] and Cmax [Bottom]) in Virtual Pediatric Population Following Recommended IMI/REL Dosing Regimen Administration and in Studied Pediatric Patients and Adult Patients Following Protocol-Based (for Pediatrics) and Approved (500/250 mg for Adults) IMI/REL Dosing Regimen Administration Stratified by Age Categories





Source: simulations-virtual-poppk-imi-rel-peds-vs-adult-ref-normal-renal-v10-pdose-30kg-q8hc5.html
Notes: Boxplots represent the simulated pediatric exposures; 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; Cmax=maximum concentration; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI/REL=imipenem/cilastatin/relebactam combination; max=maximum; min=minimum; PPK=population pharmacokinetics; REL=relebactam

The CHMP noted that for AUC, for both IMI and REL, the simulated box plot exposure is similar to adult reference exposure with a trend to slightly higher AUC in younger children. For C_{max}, except for adolescents, the C_{max} appear slightly higher in children compared to adults. Paediatric subjects are dosed with a 60-minute infusion rather than a 30-minute infusion. The MAH chose 60 minutes infusion time to avoid even higher C_{max} in children. The considered that overall, the paediatric exposure is a good match.

Given that the insufficient paediatric data to identify differences in PK by infection type, simulations for HABP/VABP paediatric patients was conducted using fixed pneumonia effects from adult analysis which is considered appropriate. The HABP/VABP simulated exposure are largely overlapping with cUTI/cIAI simulated exposure. Probability of target attainment simulations have also been provided, further supporting the adequacy of the dosing, with regards to efficacy (see next section below).

2.5.2. Pharmacodynamics

IMI/REL is a carbapenem BL/BLI combination that has potent activity against class A/C β lactamases including PDC and KPC. It is active against the majority of NME spp., including most ESBL-producing strains, and has demonstrated efficacy in animal infection models. The activity of IMI/REL, and imipenem alone, has been well characterised in a comprehensive series of in vivo and in vitro microbiology studies provided in the original marketing application. No new in vivo or in vitro studies were performed in support of this paediatric submission.

2.5.3. PK/PD modelling

Probability of target attainment

The PK/PD indices for IMI and REL best correlating effect have previously been determined as time above MIC (% *f*T>MIC) and free $AUC_{0\text{-}24h}$ over MIC (*f*AUC/MIC), respectively.

The aim of the PTA analysis was to determine the percentage of patients that met the established targets for both REL ($fAUC_{0\text{-}24h}$/MIC, above threshold of 8) and imipenem (free imipenem concentration

above the MIC for at least 40% of time during a dose interval) at steady-state. Unbound (free) fractions of 80% of imipenem and 78% of REL were used.

For the PTA simulations, a virtual paediatric population was constructed by sampling from the National Health and Nutrition Examination Survey database (https://wwwn.cdc.gov/nchs/nhanes/nhanes3/datafiles.aspx) to obtain demographic (age and weight) data comparable to the studied population in clinical trials. In addition to age and body weight, to complement the virtual population, bedside Schwartz eGFR values were randomly sampled using the median and interquartile range of eGFR based on the bedside Schwartz equation (EGFRBS) from Study P021 study participants. The simulated eGFR values were then truncated between 90 mL/min/1.73 m2 and the 97.5th percentile of Study P021 eGFR distribution (232 mL/min/1.73 m2) to obtain a virtual paediatric population with normal renal function. In total, 10000 virtual paediatric patients (N=2000 for each age cohort) were created. The same 10000 virtual paediatric patients were used for both cIAI/cUTI and HABP/VABP simulations. Demographic summaries of the virtual paediatric population are provided in [Table 14].

Table 14 Descriptive Summary of Demographics of the Virtual Pediatric Population Generated for the Simulations Stratified by Age Cohort

	Birth to <3 Mo (N=2000)	≥ 3 Mo to <2 Yrs (N=2000)	≥ 2 Yrs to <6 Yrs (N=2000)	≥ 6 Yrs to <12 Yrs (N=2000)	≥12 Yrs to <18 Yrs (N=2000)	Overall (N=10000)
Weight (kg)						
Mean (SD)	4.41 (0.868)	9.97 (2.91)	17.2 (3.98)	34.9 (12.7)	63.8 (18.6)	26.0 (23.8)
Median [Min, Max]	4.29 [2.38, 8.72]	9.88 [3.87, 28.5]	16.4 [9.80, 34.9]	31.9 [14.7, 113]	60.2 [29.0, 154]	16.7 [2.38, 154]
Age (yrs)						
Mean (SD)	0.124 (0.0727)	1.13 (0.512)	3.38 (1.14)	8.42 (1.72)	14.4 (1.68)	5.49 (5.44)
Median [Min, Max]	0.126 [0.000139, 0.250]	1.13 [0.251, 2.00]	3.00 [2.00, 5.00]	8.00 [6.00, 11.0]	14.0 [12.0, 17.0]	3.00 [0.000139, 17.0]
eGFR-Bedside Schwartz (mL/min/1.73 m^2)						
Mean (SD)	n/a	n/a	133 (27.4)	133 (26.2)	131 (26.2)	132 (26.6)
Median [Min, Max]	n/a	n/a	129 [90.1, 227]	130 [90.0, 232]	128 [90.0, 227]	129 [90.0, 232]

Source: mk-7655a-simulation-pediatric-virtual-patients-create-v7.html
eGFR values were not taken into account in pediatric patients younger than 2 years of age, because changes in renal clearance were accounted for using the maturation function proposed by Rhodin et al.
Abbreviations: eGFR=estimated glomerular filtration rate; Max=maximum; Min=minimum; mo=months; N=number of participants; n/a=not applicable; SD=standard deviation; yrs=years

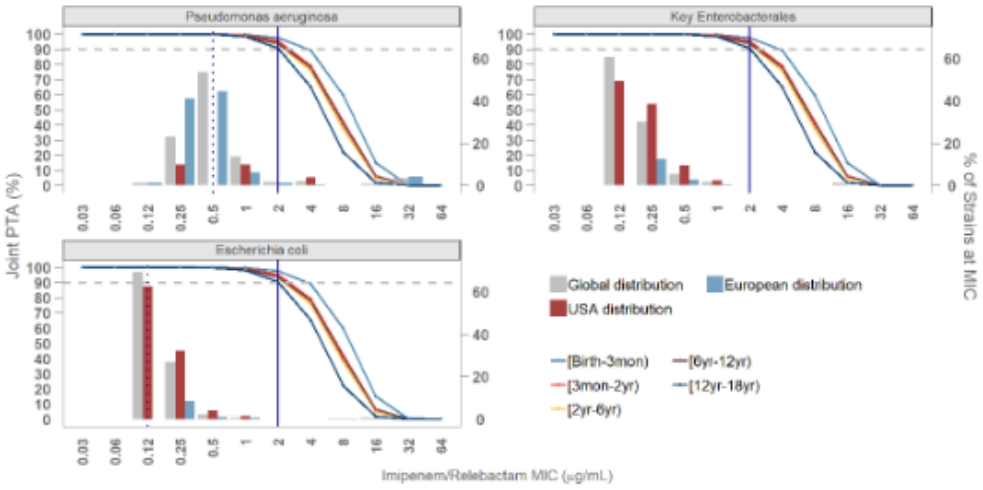
PTA simulations were performed based on a target of 40% fT>MIC for imipenem and fAUC/MIC=8.0 for REL. All age categories achieved the joint PTA target at an MIC value of 2 µg/mL. The simulated percentage of cIAI/cUTI population stratified by age categories achieving these targets is summarised in [Table 15] and PTA plots are presented in [Figure 11].

Table 15 Percentage of cIAI/cUTI Virtual Pediatric Patients Following Recommended IMI/REL Dosing Regimen Administration Achieving 40% fT>MIC for Imipenem and fAUC/MIC=8.0 for REL at Steady-State Stratified by Age Cohorts

	Percentage of Patients Achieving PTA Versus Various MIC (µg/mL) Levels											
Cohort	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
≥12 yrs to <18 yrs	100	100	100	100	99.95	98.25	90.70	65.30	22.10	1.80	0.00	0
≥6 yrs to <12 yrs	100	100	100	100	99.95	99.00	93.85	78.15	40.70	6.50	0.00	0
≥2 yrs to <6 yrs	100	100	100	100	99.90	99.00	93.50	76.10	37.70	4.95	0.00	0
≥3 mo to <2 yrs	100	100	100	100	99.95	99.35	95.40	79.30	42.15	6.25	0.05	0
≥Birth to <3 mo	100	100	100	100	100.00	99.75	97.65	89.40	59.85	15.00	0.20	0

Source: mk-7655a-simulation-pediatric-run1509-2509-report-v10-pdose-30kg-q8hc5.html
Abbreviations: % *f*T>MIC=percent unbound time above MIC; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; *f*AUC/MIC=unbound area under the concentration-time curve over MIC; IMI/REL=imipenem/cilastatin/relebactam combination; MIC=minimum inhibitory concentration; PTA=probability of target attainment; REL=relebactam

Figure 11 Percentage of cIAI/cUTI Virtual Pediatric Patients Following Recommended IMI/REL Dosing Regimen Administration Achieving 40% fT>MIC for Imipenem and fAUC/MIC=8.0 for REL at Steady-State Stratified by Age Cohorts



Source: mk-7655a-simulation-pediatric-run1509-2509-report-v10-pdose-30kg-q8hc5.html
Dashed horizontal line represents 90% PTA; solid vertical line represents MIC=2 µg/mL; dotted vertical line represents median MIC from Study P021 for available pathogens.
Abbreviations: % *f*T>MIC=percent unbound time above MIC; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; *f*AUC/MIC=unbound area under the concentration-time curve over MIC; IMI/REL=imipenem/cilastatin/relebactam combination; MIC=minimum inhibitory concentration; PTA=probability of target attainment; REL=relebactam; USA=United States of America

PTA HABP/VABP

PTA simulations were also performed for HABP/VABP infection based on a target of 40% fT>MIC for imipenem and fAUC/MIC=8.0 for REL. All age categories achieved the joint PTA target at an MIC value of 2 µg/mL. The simulated percentage of HABP/VABP infection stratified by age categories and dose groups achieving these targets is summarised in [Table 16].

Table 16 Percentage of HABP/VABP Virtual Pediatric Patients Following Recommended IMI/REL Dosing Regimen Administration Achieving 40% fT>MIC for Imipenem and fAUC/MIC=8.0 for REL at Steady-State Stratified by Age Cohorts

	Percentage of Patients Achieving PTA Versus Various MIC (µg/mL) Levels											
Cohort	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
≥12 yrs to <18 yrs	100	100	100	100	99.95	99.85	97.95	88.00	54.80	13.25	0.50	0.0
≥6 yrs to <12 yrs	100	100	100	100	100.00	99.75	98.85	92.50	70.75	27.10	2.55	0.0
≥2 yrs to <6 yrs	100	100	100	100	100.00	99.95	99.35	93.00	68.30	24.75	1.80	0.0
≥3 mo to <2 yrs	100	100	100	100	100.00	100.00	99.40	95.00	76.40	30.25	1.90	0.0
≥Birth to <3 mo	100	100	100	100	100.00	100.00	99.75	97.95	86.30	49.60	8.20	0.1

Source: mk-7655a-simulation-pediatric-run1509-2509-report-v10-pdose-30kg-q8hc5.html
Abbreviations: % *f*T>MIC=percent unbound time above MIC; *f*AUC/MIC=unbound area under the concentration-time curve over MIC; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; IMI/REL=imipenem/cilastatin/relebactam combination; MIC=minimum inhibitory concentration; PTA=probability of target attainment; REL=relebactam

The CHMP noted that the MAH constructed a virtual paediatric population using the Health and Nutrition Examination Survey database. 10,000 subjects (2,000 per cohort) were included. This approach is considered appropriate. For renal impairment simulations, a uniform distribution of eGFR was used, this is considered appropriate for RI.

The CHMP considered that PTA simulations support that for MIC up to 2 ug/mL, the proposed dosing is appropriate. This is in line with the adult breakpoint.

A HABP VABP covariate effect was not included in the IMI and REL final models. However, the MAH simulated PTA for cUTI/cIAI as well as for HABP/VABP. For HABP/VABP. the adult covariate effect for HABP/VABP was used. The exposure is higher for HABP/VABP, and thus the PTA is higher. Overall, the CHMP was of the view that PTA simulations support the proposed dosing.

Renal impairment PTA

PTA simulations were conducted to evaluate potential dosing adjustments in paediatric patients with RI. The virtual paediatric population described in was used also to support the RI simulations. For the RI simulations, eGFR was sampled using a uniform distribution for each RI category. RI was evaluated in 2 specific subgroups:

- cIAI/cUTI or HABP/VABP paediatric patients ≥30 kg and <18 years
- cIAI/cUTI or HABP/VABP paediatric patients <30 kg and ≥2 years

Proposed dosing recommendations for paediatric patients ≥30 kg and <18 years with normal renal function are identical to that approved for adults, therefore, renal-based adjustments identical to those in adults for each category of RI were expected to achieve similar exposures in paediatric and adult patients with RI compared to adults with normal renal function.

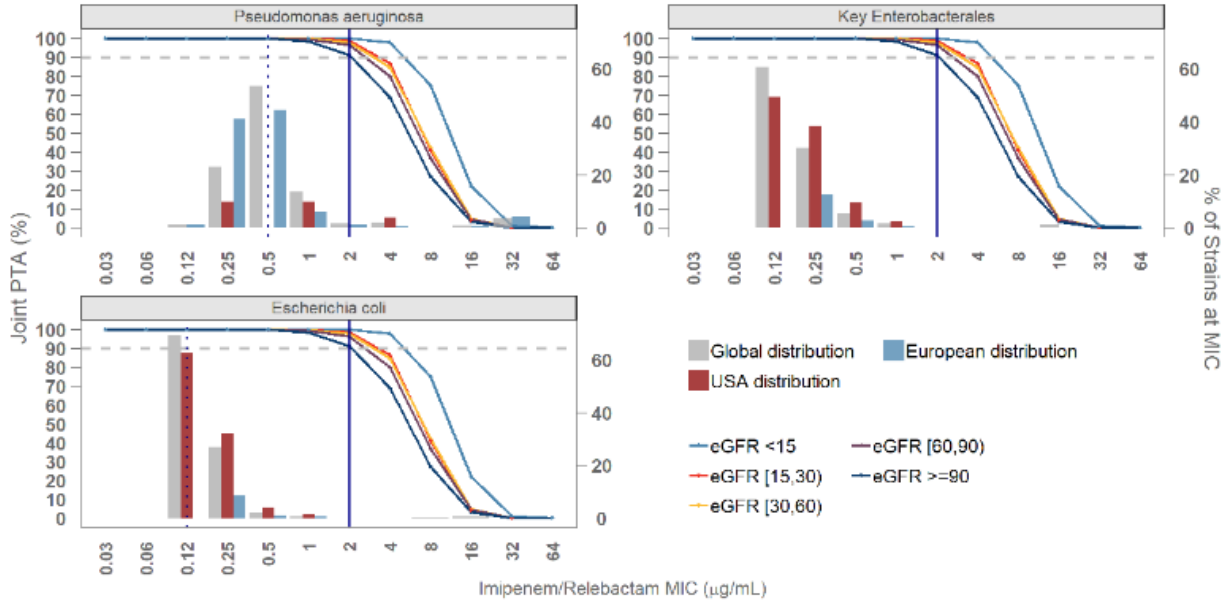
Simulation results in virtual paediatric patients ≥30 kg and <18 years with mild, moderate, and severe renal impairment and ESRD receiving the adjusted dosing recommendations as approved in adults confirmed adequate exposures to maintain sufficient joint PTA across all RI categories. Results for both imipenem and REL remain comparable to both adult patients with normal renal function as well as adult patients with various degrees of RI.

Table 17 Percentage of cIAI/cUTI Virtual Pediatric RI Population ≥30 kg and <18 Years Following Adjusted IMI/REL Dosing Regimen Administration Achieving 40% fT>MIC for Imipenem and fAUC/MIC=8.0 for REL at Steady-State Stratified by RI Categories

	Percentage of Patients Achieving PTA Versus Various MIC (µg/mL) Levels											
RI category	**0.03**	**0.06**	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**64**
eGFR <15	100	100	100	100	100.00	100.00	99.97	97.88	75.12	22.12	1.14	0
eGFR [15,30)	100	100	100	100	100.00	99.90	98.83	86.78	41.20	4.06	0.03	0
eGFR [30,60)	100	100	100	100	100.00	99.90	97.97	84.75	42.28	4.75	0.03	0
eGFR [60,90)	100	100	100	100	99.94	99.46	96.42	80.06	36.96	4.47	0.06	0
eGFR ≥90	100	100	100	100	99.97	98.48	91.35	69.00	27.23	3.20	0.00	0

Source: mk-7655a-simulation-pediatric-run1509-2509-report-v10-over30kg-addose-ri.html
Abbreviations: % *f*T>MIC=percent unbound time above MIC; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; eGFR=estimated glomerular filtration rate; *f*AUC/MIC=unbound area under the concentration-time curve over MIC; IMI/REL=imipenem/cilastatin/relebactam combination; MIC=minimum inhibitory concentration; PTA=probability of target attainment; REL=relebactam; RI=renal impairment

Figure 12 Percentage of cIAI/cUTI Virtual Pediatric RI Population ≥30 kg and <18 Years Following Adjusted IMI/REL Dosing Regimen Administration Achieving 40% fT>MIC for Imipenem and fAUC/MIC=8.0 for REL at Steady-State Stratified by RI Categories



Source: mk-7655a-simulation-pediatric-run1509-2509-report-v10-over30kg-addose-ri.html
Notes: Dashed horizontal line represents 90% PTA; solid vertical line represents MIC=2 µg/mL; dotted vertical line represents median MIC from Study P021 for available pathogens.
Abbreviations: % *f*T>MIC=percent unbound time above MIC; cIAI/cUTI=complicated intra-abdominal infection/complicated urinary tract infection; eGFR=estimated glomerular filtration rate; *f*AUC/MIC=unbound area under the concentration-time curve over MIC; IMI/REL=imipenem/cilastatin/relebactam combination; MIC=minimum inhibitory concentration; PTA=probability of target attainment; REL=relebactam; RI=renal impairment; USA=United States of America

The CHMP noted that the proposed dosing recommendations for paediatric patients ≥30 kg and <18 years are the same as the dosing approved for adults. The MAH provided PTA simulations to support the dosing. Adolescents/children weighing at least 30 kg are expected to be similar to adults. Thus, the CHMP considered the proposed dosing to be supported.

The MAH also discussed children 2-17 years below 30 kg but concluded that no dose adjustment can be made and this is in line with the imipenem labelling.

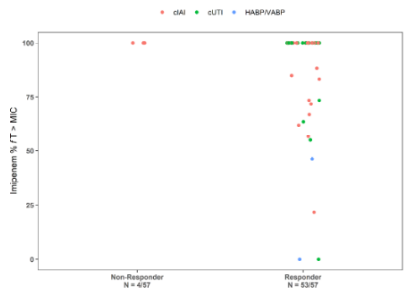
For mild renal impairment in adults, only around a 20% increase in exposure of IMI/REL is seen and the dose is adjusted accordingly. For children 2 years and older, maturation of kidney function is not expected to be a confounding factor. Thus, considering the modest change in exposure of IMI/REL with mild RI in adults, the MAH was asked to consider and discuss if a dosing recommendation (similar magnitude of dose reduction as in adults or no dose adjustment) for mild RI could be recommended for children of at least 2 years of age, weighing below 30 kg. The MAH maintained that IMI/REL should not be recommended for paediatric patients weighing less than 30 kg with renal impairment due to a lack of clinical and PK data in this population. Imipenem, cilastatin, and REL are all known to be substantially excreted by the kidneys, and the risk of developing adverse reactions to them may be greater in patients with impaired renal function. This was considered acceptable by the CHMP.

Exposure-response analyses

Only participants from Study P021 who were treated with IMI/REL IV infusion were included

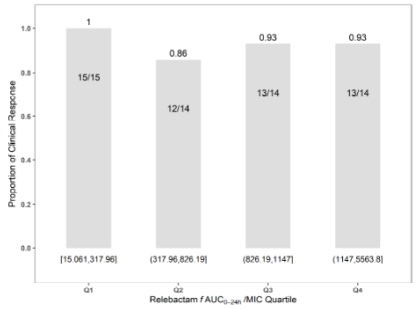
in this exploratory analysis. Of the 57 participants with a baseline microbiological response, 53 (93.0%) demonstrated a favourable clinical response (defined as cure or sustained cure) at EOT, and 48 (84.2%) maintained this response at EFU. For microbiological response, a favourable outcome was observed in 55 (96.5%) participants at EOT, and in 50 (87.7%) participants at EFU the response was maintained.

Figure 13 Relationship Between %fT>MIC and Clinical Response at EOT to Imipenem



Source: er.efficacy.html
Notes: Imipenem %fT>MIC at EOT were derived from 57 participants.
Abbreviations: %fT>MIC=percent free time above minimum inhibitory concentration; cIAI=complicated intra-abdominal infection; cUTI=complicated complicated urinary tract infection; EOT=end of treatment; HABP/VABP=hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; N=number of participants

Figure 14 Proportion of Participants Achieving Clinical Response Across fAUC.sa/MIC Quartiles at EOT to REL



Source: er.efficacy.html
Notes: Relebactam $fAUC_{0\text{-}24h}$/MIC quartiles were derived from 57 participants [exposure range in square brackets] at EOT. Participant numbers with a favorable clinical response out of the total is shown within the bar, and the resulting proportion is indicated at the top of the bar.
Abbreviations: EOT=end of treatment; $fAUC_{0\text{-}24h}$/MIC=unbound area under the plasma concentration-time curve from time zero to 24 hours over MIC; MIC=minimum inhibitory concentration; N=number of participants; Qx=Quartile x; REL=relebactam

Overall, the lack of trends observed between imipenem and REL exposure or MIC-related metrics and efficacy endpoints suggesting that adequate efficacy is achieved. Since the exploratory analysis did not reveal any apparent trends, a model-based analysis was not conducted.

Similarly, no AE or severe AE relationship was found with exposure (not shown).

2.5.4. Discussion on clinical pharmacology

popPK models

The paediatric PK dataset includes both single dose and multiple dose data from 2 paediatric studies. 27 subjects from birth to less than 3 months are included in the dataset with 14 subjects below 1 month of age and thus an indication down to birth is considered appropriate.

Based on the observed data figure, exposure of IMI and REL for cUTI/cIAI, HABP/VABP and other infections subjects are largely overlapping. The majority of paediatric data are from cUTI/cIAI subjects.

Separate models were developed for IMI and REL. The adult 2-compartment models for IMI and REL were used as starting points.

The RSEs for the final model IMI are reasonable. The GOF plots do not indicate any major misspecification. pcVPC were provided both stratified on age and on body weight. Generally, the IMI pcVPCs support that the model can adequately describe the data. For some of the pcVPCs, several observations are not within the plotted bins. The simulated 5th percentile also appears to be systematically below the observed 5th percentile. Simulating slightly lower exposure is considered conservative with regards to efficacy and probability of target attainment. Similar issues with the pcVPCs and with lower 5th percentile is seen for relebactam. The GOF and pcVPCs indicate that both the IMI and the REL popPK models are fit for purpose.

The corresponding adult popPK models includes disease/indication as a covariate. In contrast, the paediatric PopPK models do not include disease/indication as a covariate which is a limitation/uncertainty of the presented paediatric PopPK model. The MAH should provide additional goodness-of-fit plots to confirm whether there are any meaningful model misspecifications regarding disease/indication as a potential covariate. The MAH provided eta-vs-covariate plots for eta associated with CL vs the categorical covariate disease/indication. The provided figures do not indicate any relationship between major infection types (i.e., cUTI, cIAI, HABP/VABP).

Model derived exposure of IMI/REL

The models were used to simulate AUC and C_{max}, as well as PTA. For AUC, for both IMI and REL, the simulated box plot exposures are similar to adult reference exposure with a trend towards slightly higher AUC in younger children. The C_{max} appears slightly higher in children <12 years of age compared to adults. Paediatric subjects are dosed with a 60-minute infusion rather than 30 minutes. The MAH chose 60-minute infusion time to avoid even higher C_{max} in children. Overall, the paediatric exposure is considered to match well based on the provided figures.

PTA

Probability of target attainment simulations have also been provided to further support the adequacy of the dosing, with regards to efficacy.

The MAH has constructed a virtual paediatric population using the Health and Nutrition Examination Survey database. 10000 subjects (2000 per cohort) were included. This approach is considered appropriate. For renal impairment simulations, a uniform distribution of eGFR was used, this is considered appropriate for RI.

The PTA simulations for cUTI/cIAI paediatric subjects support that for MIC up to 2 ug/mL, hence the proposed dosing is appropriate. This is in line with adult breakpoint. A HABP VABP covariate effect was not included in the IMI and REL final models. However, the MAH simulated PTA using the adult covariate effect for HABP/VABP. The exposure is higher, and therefore the PTA is higher. Overall, the PTA simulations support the proposed dosing.

Renal impairment

The proposed dosing recommendations for paediatric patients ≥30 kg and <18 years with normal renal function and renal impairment are the same to that approved for adults. The MAH provided PTA simulations to support the dosing. Adolescents/children weighing at least 30 kg are expected to be similar to adults. Thus, the proposed dosing is supported.

For mild renal impairment in adults, only around a 20% increase in exposure is seen and the IMI/REL dose is adjusted accordingly. For children 2 years and older, maturation of kidney function is not expected to be a confounding factor. Further, considering the modest change in exposure of IMI/REL with mild RI in adults, the MAH was asked to consider and discuss if a dosing recommendation (similar to adults or no dose adjustment) for mild RI could be recommended for children of at least 2 years of age, weighing below 30 kg. The MAH maintains that IMI/REL should not be recommended for paediatric patients weighing less than 30 kg with renal impairment due to a lack of clinical and PK data in this population.

2.5.5. Conclusions on clinical pharmacology

The popPK models for imipenem for relebactam are both considered adequate. The popPK dataset includes children from birth and an indication from birth can be supported. The dosing is supported both by similar exposure of IMI and REL compared to adults as well as probability of target attainment simulations. The infusion time has been increased (50-60 minutes compared to 30 minutes) in children compared to adults to avoid too high C_{max}. Overall, the proposed dosing in children with normal renal function is supported.

For children weighing at least 30 kg, the same dose adjustments as in adults is proposed regarding RI and this is supported. For children below 30 kg, no recommendation regarding RI have been provided.

Overall, extrapolation from adults to children, supported by similar exposure in adults and children as well as PTA simulations, can be supported.

The activity of IMI/REL, and imipenem alone, has been previously well characterised in a comprehensive series of in vivo and in vitro microbiology studies provided in the original marketing application. No new pharmacodynamic studies were performed in support of this paediatric submission.

2.6. Clinical efficacy

2.6.1. Dose response studies

Initial and final dose determination for the paediatric population was based on modelling and simulation informed by paediatric PK data from 2 clinical studies: a single-dose Phase 1 study (P020) and a multiple dose Phase 2/3 study (P021). See 2.5. Pharmacokinetics above.

The supportive Phase 1b study, P020, evaluated the PK, safety, and tolerability of a single dose of IMI/REL did not evaluate efficacy.

2.6.2. Main study

The only available paediatric efficacy data for IMI/REL in the sought indication are descriptive in nature and come from a single Phase 2/3 study (P021) in paediatric participants from birth to <18 years of age with confirmed or suspected gram-negative bacterial infections (HABP/VABP, cIAI, or cUTI).

P021: A Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Paediatric Participants From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection

EudraCT: 2019-000338-20, NCT03969901

Methods

Study participants

Male or female participants from birth to less than 18 years of age who required hospitalisation and treatment with IV antibacterial therapy for confirmed or suspected gram-negative bacterial infection (in the absence of meningitis) involving 1 of 3 primary infection types: HABP/VABP, cUTI, or cIAI. Enrolment targets were set to ensure sufficiently proportionate enrolment across the infection types.

Five paediatric age cohorts were to be evaluated in the study:

- Age Cohort 1: Adolescents (12 to <18 years)
- Age Cohort 2: Older Children (6 to <12 years)
- Age Cohort 3: Younger Children (2 to <6 years)
- Age Cohort 4: Infants and Toddlers (3 months to <2 years)
- Age Cohort 5: Neonates and Young Infants (birth to <3 months)

Main inclusion/exclusion criteria

Inclusion (non-exhaustive):

- ✓ Male or female from birth to less than 18 years of age.
- ✓ For Age Cohorts 4 and 5: at least 37 weeks postmenstrual age.
- ✓ Required hospitalisation and treatment with IV antibacterial agent therapy for confirmed or suspected gram-negative bacterial infection (in the absence of meningitis) and was expected to require hospitalisation through completion of IV study intervention, with at least 1 of the following primary infection types as defined in the protocol - HABP or VABP - cIAI – cUTI.

Exclusion (non-exhaustive):

- × Expected to survive less than 72 hours.
- × Concurrent infection listed in the protocol that would interfere with evaluation of response.
- × Concomitant infection that required non-study systemic antibacterial agent therapy (medications with only gram-positive activity [e.g., vancomycin, linezolid] were allowed).
- × Had HABP/VABP caused by an obstructive process.
- × Had cUTI with complete obstruction of any portion of the urinary tract, reflux of ileal loop urinary diversion, perinephric or intrarenal abscess, prostatitis, urethritis, or epididymitis, trauma, indwelling urinary catheter that could not be removed at study entry.
- × History of seizure disorder or 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 for more than 24 hours during the 48 hours preceding the first dose of study intervention.
- × Anticipated to be treated with the medications identified in the protocol including concomitant IV, oral, or inhaled antimicrobial agents with gram-negative activity.
- × 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, haemodialysis, or hemofiltration.
- × ALT or AST ≥5 x ULN at the time of screening.

Treatments

IMI/REL was administered according to the following posology (60- minute infusions):

- 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

Active comparator (local Standard of Care) was not protocol-defined, but determined according to local practice and administered according to authorised Product Information or international treatment guidelines.

Total duration of study treatment of study drug or active comparator depended on site of infection:

- 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 maximum of 14 days.

Objectives and endpoints

Efficacy endpoints were secondary in this study and the study was not powered for inferential analyses.

Efficacy outcomes described below were evaluated at End of Treatment (EOT), Early Follow-up (EFU, 7 to 14 days after EOT), and Late Follow-up (LFU, 7 to 14 days after EFU) visits.

Clinical Response Categories at the EOIV and EOT Visits

Clinical Response[a]	Response Definition
Cure	All preintervention signs and symptoms[b] of the index infection have resolved (or returned to "preinfection status," with no new symptoms) **AND** no additional antibacterial intervention is required for the index infection.
Improved	The majority of preintervention signs and symptoms[b] of the index infection have improved or resolved (or returned to "preinfection status," with no new symptoms) **AND** no additional antibacterial agent intervention is required.
Failure	No apparent response to study intervention in prestudy signs and symptoms[b] of the index infection: persistence or progression of the majority of or all preintervention signs and symptoms.
Indeterminate	Study data are not available for evaluation of clinical response for any reason at the visit, including: Complication related to underlying medical condition; **OR** Participant was withdrawn for any reason before sufficient data had been obtained to permit evaluation for any reason; **OR** Extenuating circumstances (eg, an important protocol deviation) preclude classification as "cure," "improved," or "failure;" **OR** Death occurred during the study period and the index infection was clearly noncontributory.

EOIV=end of IV therapy; EOT=end of therapy.

[a] A favorable clinical response at EOT requires an assessment of "cure" or "improved."

[b] Refer to Section 8.2.2.1 and Table 5 of the protocol [16.1.1] for a description of relevant clinical signs and symptoms.

Source: Adapted from Table 6 of the protocol [16.1.1].

Clinical Response Categories at the EFU and LFU Visits

Clinical Response[a]	Response Definition
Sustained Cure	All preintervention signs and symptoms[b] of the index infection have resolved (or returned to "preinfection status," with no new symptoms) with no evidence of resurgence **AND** no additional antibacterial agent intervention is required for the index infection.
Cure	All preintervention signs and symptoms[b] of the index infection have resolved (or returned to "preinfection status," with no new symptoms) **AND** no additional antibacterial agent intervention is required for the index infection.
Failure	No apparent response or insufficient response to study intervention in prestudy signs and symptoms of the index infection: persistence, progression, or improvement (without full resolution) of all preintervention signs and symptoms.[b]
Relapse	Participants with a favorable clinical response (cure or improvement) at the EOT visit have new or worsening signs and symptoms[b] of the index infection by the EFU or LFU visit.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including: a) Complication related to underlying medical condition; **OR** b) Participant was withdrawn for any reason before sufficient data had been obtained to permit evaluation of clinical response; **OR** c) Extenuating circumstances (eg, an important protocol deviation) preclude classification as "sustained cure," "failure," or "relapse;" **OR** d) Death occurred during the study period and the index infection was clearly noncontributory.

EFU=early follow-up; EOT=end of therapy; LFU=late follow-up.

[a] A favorable clinical response at EFU or LFU requires an assessment of "cure" or "sustained cure." To be considered "sustained cure," the clinical response for the prior visit (EOT or EFU) must have been considered "cure."

[b] Refer to Section 8.2.2.1 and Table 5 of the protocol [16.1.1] for a description of clinical signs and symptoms.

Source: Adapted from Table 7 of the protocol [16.1.1].

Microbiological Response Categories 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 (reduced to $<10^3$ 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] grows the uropathogen (at $\geq 10^3$ CFU/mL) found at study entry.
Superinfection[e]	HABP/VABP: A lower respiratory tract culture taken at the EOT visit[c] 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 new or worsening signs and symptoms of infection. cIAI: An intra-abdominal culture taken at the EOIV or EOT visit[c] 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 new or worsening signs and symptoms of infection. cUTI: A urine culture taken at the EOIV or EOT visit[c] grows a uropathogen (at $\geq 10^5$ CFU/mL) 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 new or worsening signs and symptoms of infection.
Indeterminate	Follow-up culture is not available at the EOIV or EOT visit[c] due to participant death or withdrawal from study; **OR** Available microbiological data are incomplete (eg, sample collected, but no results available); **OR** Extenuating circumstances (eg, an important protocol deviation) preclude microbiological assessment; **OR** Any other circumstance which makes it impossible to define the microbiological response.

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.
e	For cUTI, if sterile urine collection bag method is used for post-baseline sampling, see Section 8.2.3.1.3 of the protocol [16.1.1].

Source: Adapted from Table 8 of the protocol [16.1.1].

Microbiological Response Categories 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 (reduced to <103 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	HABP/VABP: A lower respiratory tract culture taken at the EFU or LFU visit grows the pathogen found at study entry. cIAI: An intra-abdominal culture taken at the EFU or LFU visit[c] grows the pathogen found at study entry. cUTI: A urine culture taken at the EFU or LFU visit[c] grows the uropathogen (at ≥103 CFU/mL) found at study entry.
New Infection[d]	HABP/VABP: A pathogen other than an original microorganism found at study entry is present in the lower respiratory tract culture 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. cIAI: A pathogen other than an original microorganism found at study entry is present in the intra-abdominal culture 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. cUTI: A urine culture grows a uropathogen (at ≥105 CFU/mL) other than a baseline pathogen after the completion of IV or oral study intervention, **OR** emergence after the completion of IV or oral study intervention of a new pathogen at a distant sterile site along with new and/or worsening signs and symptoms of infection.
Recurrence[d]	HABP/VABP: A lower respiratory tract culture grows the baseline pathogen taken any time after documented eradication. cIAI: An intra-abdominal culture grows the baseline pathogen taken any time after documented eradication. cUTI: A urine culture grows the baseline uropathogen (at ≥105 CFU/mL) 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 (eg, sample collected, but no results available); **OR** c) Extenuating circumstances (eg, an important protocol deviation) preclude microbiological assessment; **OR** d) Any other circumstance which makes it impossible to define the microbiological response.

CFU=colony-forming unit; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EFU=early follow-up; EOT=end of therapy; 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.

[d] For cUTI, if sterile urine collection bag method is used for post-baseline sampling, see Section 8.2.3.1.3 of the protocol [16.1.1].

Source: Adapted from Table 9 of the protocol [16.1.1].

Sample size

The planned overall enrolment for P021 was approximately 140 participants across 5 age cohorts but was subsequently reduced to 115 participants across 5 age cohorts, following slower than anticipated enrolment into Age Cohorts 4 and 5. Sample size was determined by the safety and PK objectives.

Age Cohort 1: Adolescents (12 to <18 years) - No more than 12 participants

- Age Cohort 2: Older Children (6 to <12 years) - At least 20 participants
- Age Cohort 3: Younger Children (2 to <6 years) - At least 20 participants
- Age Cohort 4: Infants and Toddlers (3 months to <2 years) - At least 28 participants
- Age Cohort 5: Neonates and Young Infants (birth to <3 months) - At least 28 participants

Randomisation

Participants with HABP/VABP, cIAI, or cUTI were randomised in a 3:1 ratio to receive IMI/REL or active control. Participants were stratified by age group and infection type prior to randomisation.

Blinding (masking)

This was an open-label study.

Statistical methods

Descriptive statistics. There were no formal statistical hypotheses evaluated in this study.

Within-group 95% confidence intervals were calculated using the Agresti & Coull method and between-treatment difference 95% confidence intervals using the unstratified Miettinen and Nurminen method.

Results

Participant flow

A total of 130 participants were screened across 38 study sites in 18 countries. Of these, 115 participants were randomised across 35 study sites in 15 countries, while 15 participants did not meet study criteria.

In the All Randomised Participants population:

• IMI/REL group: 86 randomised, 85 treated, 72 completed treatment, 13 discontinued treatment, 84 completed study, 2 discontinued study.

• Active Control group: 29 randomised, 28 treated, 23 completed treatment, 5 discontinued treatment, 28 completed study, 1 discontinued study.

Recruitment

First Participant First Visit 08-OCT-2019

Last Participant Last Visit 07-MAY-2024

Last Data Available 12-JUL-2024

Database Lock Date 19-JUL-2024

Conduct of the study

The protocol was subject to 5 amendments, none of which constituted a substantial material change to the design of the study or interpretation of results.

A total of 67 clinical investigator study sites were located in 18 countries: Bulgaria, Chile, Colombia, Estonia, France, Greece, Hungary, Israel, Mexico, Norway, Philippines, Poland, Russia, South Africa, Spain, Turkey, Ukraine, and United States.

Baseline data

Demographic and baseline characteristics were generally comparable for both intervention groups.

Demographics

In the All Randomised Participants population:

Sex: Male (IMI/REL: 43 [50.0%], Active Control: 16 [55.2%]); Female (IMI/REL: 43 [50.0%], Active Control 13 [44.8%]).

Ethnicity: Not Hispanic or Latino (IMI/REL: 50 [58.1%], Active Control: 20 [69.0%]); Hispanic or Latino (IMI/REL: 34 [39.5%]; Active Control: 9 [31.0%]; Not reported (IMI/REL: 2 [2.3%], Active Control: 0 [0.0%]).

Race: White (IMI/REL: 72 [83.7%]; Active Control: 22 [75.9%]); Multiple (IMI/REL: 8 [9.3%]; Active Control: 4 [13.8%]); Black or African American (IMI/REL: 3 [3.5%]; Active Control: 1 [3.4%]); American Indian or Alaska native (IMI/REL: 3 [3.5%]; Active Control: 1 [3.4%]); Asian (IMI/REL: 0 [0.0%]; Active Control: 1 [3.4%]).

Infection type: cUTI (IMI/REL: 41 [47.7%]; Active Control: 14 [48.3%]); cIAI (IMI/REL:40 [46.5%]; Active Control: 14 [48.3%]); HABP/VABP (IMI/REL: 5 [5.8%]; Active Control: 1 [3.4%]).

Medical history

Baseline intra-abdominal surgical procedures were generally comparable for both intervention groups.

Medical history conditions in the All Participants Randomised population were generally comparable for both intervention groups by infection type.

The types of prior and concomitant medications reported were as expected for hospitalised paediatric participants with gram-negative bacterial infections with most (≥85%) participants having received ≥1 prior and concomitant medication. The frequency of reported prior and concomitant medications (including anti-infective medications) were generally comparable for both the IMI/REL and Active Control groups.

Microbiology

The most common baseline pathogens from infection site cultures in the IMI/REL group (>5% of participants) were *Escherichia coli* (48 participants [70.6%]), *Pseudomonas aeruginosa* (12 [17.6%]), *Klebsiella pneumoniae* (4 [5.9%]), and *Bacteroides fragilis* (4 [5.9%]), and in the Active Control group (>5% of participants) *E. coli* (16 participants [72.7%]), *P. aeruginosa* (3 [13.6%]), and *B. fragilis* (3 [13.6%]).

Only one of the 90 participants in the mMITT population had a baseline key pathogen from blood culture (*K pneumoniae*, IMI/REL group).

Of the baseline qualifying pathogens from primary site isolates in the mMITT population, susceptibility (according to EUCAST breakpoint 2mg/L) to imipenem/REL was generally comparable for the IMI/REL (76.3% of pathogens) and Active Control (71.0%) groups.

Numbers analysed

The efficacy analyses were based on the MITT and mMITT populations.

The MITT population included all randomised participants who received at least 1 dose of IV study intervention.

The mMITT population included all randomised participants with culture-confirmed Gram-negative infection who received at least 1 dose of IV study intervention. Twenty-three randomised participants (20.0%) had a baseline culture that did not meet culture identification requirements for inclusion.

Participant Accounting by Analysis Population
All Participants Randomized

	IMI/REL		Active Control		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	86		29		115	
All Participants as Treated						
Yes	85	(98.8)	28	(96.6)	113	(98.3)
No	1	(1.2)	1	(3.4)	2	(1.7)
Withdrawal By Parent/Guardian	1	(1.2)	1	(3.4)	2	(1.7)
Modified Intent-To-Treat						
Yes	85	(98.8)	28	(96.6)	113	(98.3)
No	1	(1.2)	1	(3.4)	2	(1.7)
Withdrawal By Parent/Guardian	1	(1.2)	1	(3.4)	2	(1.7)
Microbiological Modified Intent-To-Treat						
Yes	68	(79.1)	22	(75.9)	90	(78.3)
No	18	(20.9)	7	(24.1)	25	(21.7)
Not in Modified Intent-to-Treat	1	(1.2)	1	(3.4)	2	(1.7)
Baseline Culture Did Not Meet Culture and Identification Requirements for Inclusion[a]	17	(19.8)	6	(20.7)	23	(20.0)

[a] For participants with HABP/VABP and cIAI, baseline infection-site culture did not grow at least 1 gram-negative pathogenic organism. For participants with cUTI, baseline urine culture did not grow at least 1 gram-negative pathogenic organism at least ≥ 10^5 CFU/ml.
The % is based on the number of participants in the population.

Source: [P021MK7655A: adam-adsl]

Study intervention compliance was high (>95%) and generally comparable for both intervention groups by infection type. A higher percentage of participants with HABP/VABP (100%) and cIAI (92.5%) infection type completed study medication compared with participants with cUTI (74.1%). The most common reasons for discontinuing study intervention were "other" in the IMI/REL group (7.1%, all cUTI) and "adverse event" and "physician decision" (each 7.1%) in the Active Control group.

Outcomes and estimation

Secondary efficacy analyses (non-exhaustive)

All-cause Mortality Through Day 28 (MITT)

No participants died in either intervention group in the study through Day 28.

Clinical Response at the EOT, EFU, and LFU Visits (MITT and mMITT)

Analysis of Clinical Response by Visit – All Infection Types
Modified Intent-To-Treat Population

	IMI/REL			Active Control			Difference in % vs Active Control	
	n	%	(95% CI)[c]	n	%	(95% CI)[c]	%	(95% CI)[d]
Participants in population	85			28				
EOT								
Favorable[a]	67	78.8	(68.9, 86.2)	21	75.0	(56.4, 87.6)	3.8	(-12.3, 23.9)
Cure	57	67.1		20	71.4			
Improvement	10	11.8		1	3.6			
Unfavorable	18	21.2		7	25.0			
Failure	1	1.2		0	0.0			
Indeterminate[e]	17	20.0		7	25.0			
EFU								
Favorable[b]	60	70.6	(60.1, 79.3)	21	75.0	(56.4, 87.6)	-4.4	(-21.1, 16.1)
Sustained cure	53	62.4		20	71.4			
Cure	7	8.2		1	3.6			
Unfavorable	25	29.4		7	25.0			
Relapse	4	4.7		0	0.0			
Failure	1	1.2		0	0.0			
Indeterminate[e]	20	23.5		7	25.0			
LFU								
Favorable[b]	59	69.4	(58.9, 78.2)	21	75.0	(56.4, 87.6)	-5.6	(-22.3, 15.0)
Sustained cure	57	67.1		21	75.0			
Cure	2	2.4		0	0.0			
Unfavorable	26	30.6		7	25.0			
Relapse	4	4.7		0	0.0			
Failure	1	1.2		0	0.0			
Indeterminate[e]	21	24.7		7	25.0			

EOT = end of therapy; EFU = early follow-up; LFU = late follow-up.

[a] A favorable clinical response at EOT requires an assessment of "cure" or "improved".

[b] A favorable clinical response at EFU or LFU requires an assessment of "cure" or "sustained cure". To be considered "sustained cure", the clinical response for the prior visit (EOT or EFU) must have been considered "cure".

[c] 95% confidence intervals are based on Agresti & Coull method.

[d] 95% confidence intervals are based on unstratified Miettinen & Nurminen method.

[e] Study data were not available for evaluation of the clinical response for any reason at the visit, including withdrawal of consent or extenuating circumstances (e.g., discontinuation of study medication, microbiological criteria not met, receipt of prohibited non-study antibiotics, new infection, or superinfection).

The % is based on the number of participants in the population.

Source: [P021MK7655A: adam-adsl; adefl]

The percentage of participants who achieved a favourable clinical response at the EOT, EFU, and LFU visits was comparable for both intervention groups.

The percentage of participants who achieved a favourable clinical response at the EOT, EFU, and LFU visits was numerically higher for the mMITT (not shown here) compared with the MITT population for both intervention groups.

Comparisons between individual age cohorts and between infection types are hampered by the very small sub-group sizes and should be interpreted with caution, but the percentage of participants who

achieved favourable clinical response at EOT, EFU and LFU visits was generally numerically comparable for both intervention groups across age cohorts and within infection types (not shown here).

Microbiological Response at the EOT, EFU, and LFU Visits (mMITT)

Analysis of Overall Microbiological Response by Visit – All Infection Types
Microbiological Modified Intent-To-Treat Population

	IMI/REL			Active Control			Difference in % vs Active Control	
	n	%	(95% CI)[a]	n	%	(95% CI)[a]	%	(95% CI)[b]
Participants in population	68			22				
EOT								
Favorable	65	95.6	(87.3, 99.0)	20	90.9	(71.0, 98.7)	4.7	(-5.6, 23.9)
Unfavorable	3	4.4		2	9.1			
Indeterminate	3	4.4		2	9.1			
EFU								
Favorable	58	85.3	(74.8, 92.0)	20	90.9	(71.0, 98.7)	-5.6	(-18.5, 14.4)
Unfavorable	10	14.7		2	9.1			
Indeterminate	5	7.4		2	9.1			
LFU								
Favorable	59	86.8	(76.5, 93.1)	19	86.4	(65.8, 96.1)	0.4	(-13.5, 21.3)
Unfavorable	9	13.2		3	13.6			
Indeterminate	6	8.8		2	9.1			

EOT = end of therapy; EFU = early follow-up; LFU = late follow-up.
[a] 95% confidence intervals are based on Agresti & Coull method.
[b] 95% confidence intervals are based on unstratified Miettinen & Nurminen method.
For participants from whom only 1 pathogen is isolated in the baseline infection-site culture, the microbiological response assessment will be based on the microbiological response rating for that pathogen. For participants from whom more than 1 baseline pathogen is isolated in the baseline infection-site culture, the microbiological response outcome will be based on microbiological culture results for all pathogens (ie, a "favorable" overall microbiological response requires eradication or presumed eradication of all baseline pathogens).
The % is based on the number of participants in the population.

Source: [P021MK7655A: adam-adsl; adeff]

Comparisons between individual age cohorts and between infection types are hampered by the very small sub-group sizes and should be interpreted with caution, but the percentage of participants who achieved favourable microbiological response at EOT, EFU and LFU visits was generally numerically comparable for both intervention groups across age cohorts and within infection types (not shown here).

Emergence of Non-Susceptibility to Study Interventions During IV Therapy (mMITT)

Only one participant (1.5%) in the IMI/REL group had a positive culture post baseline. No participants had emergence of non-susceptibility to imipenem/REL by both CLSI and EUCAST interpretive criteria.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study P021 was a Phase 2/3 open-label, randomised, SOC-controlled study of safety, tolerability, efficacy and pharmacokinetics of IMI/REL in 115 paediatric participants from birth to <18 years with

confirmed or suspected Gram-negative bacterial infections including cUTI, cIAI and HABP/VABP. The primary objectives were safety and PK, and efficacy endpoints were only secondary. The study was not powered for inferential analyses.

The study population, inclusion and exclusion criteria were appropriate for the objectives. Participants were randomised 3:1 to study treatment or active comparator (local Standard of Care), which was not protocol defined but determined according to local practice and administered according to authorised Product Information or international treatment guidelines. Total duration of study treatment (IV and oral step-down phases) of study drug or active comparator depended on site of infection and was appropriately defined. Main secondary efficacy endpoints were clinical cure and microbiological cure at EOT, Early Follow-up (EFU, 7 to 14 days after EOT), and Late Follow-up (LFU, 7 to 14 days after EFU) and these were appropriately defined.

Demographic and baseline characteristics were generally comparable for both intervention groups. Most randomised participants had cUTI or cIAI, with HABP/VABP comprising a minority of participants (IMI/REL: 5 [5.8%]; Active Control: 1 [3.4%]), which is perhaps not surprising.

The most common baseline pathogens from infection site cultures in the IMI/REL group (>5% of participants) were *Escherichia coli* (48 participants [70.6%]), *Pseudomonas aeruginosa* (12 [17.6%]), *Klebsiella pneumoniae* (4 [5.9%]), and *Bacteroides fragilis* (4 [5.9%]) and similar in the Active control group. Of the baseline qualifying pathogens from primary site isolates in the mMITT population, susceptibility (according to EUCAST breakpoint 2mg/L) to imipenem/REL was generally comparable for the IMI/REL (76.3% of pathogens) and Active Control (71.0%) groups.

Study intervention compliance was high (>95%) and generally comparable for both intervention groups by infection type. A higher percentage of participants with HABP/VABP (100%) and cIAI (92.5%) infection type completed study medication compared with participants with cUTI (74.1%).

Efficacy data

No participants died in either intervention group in the study through Day 28.

The majority of participants in the MITT population (>69% in both intervention groups) and in the mMITT population (>79%, in both intervention groups) achieved a favourable clinical response at the EOT, EFU, and LFU visits. The percentage of participants who achieved a favourable clinical response at the EOT, EFU, and LFU visits was numerically similar for the IMI/REL and Active Control groups.

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

Results for other secondary efficacy endpoints were supportive of the above. Comparisons between individual age cohorts and between infection types are hampered by the very small sub-group sizes and should be interpreted with caution but showed generally numerically similar results between treatment arms.

The rates of clinical failure of 4.7% (4/86) in the IMI/REL arm and 0/29 in the active control arm, and a late microbiological failure of 5.9% (4/68) in the IMI/REL arm and 4.5% (1/22) in the active comparator arm, are similar, given the small study size and thus small absolute numbers concerned. Narratives of the 7 study participants with late clinical and/or microbiological failure at EFU or LFU despite initial favourable response at EOT (not shown here) reveal that of the 6 participants on

IMI/REL with late failure, two cases of clinical and microbiological relapse of cUTI and one case of clinical relapse of cIAI were not apparently confirmed or treated with a further course of antibiotics. Meanwhile one case of clinical relapse of cUTI and one case of microbiological relapse of cUTI were confirmed to the extent that non-study antibiotic treatment was administered. One participant on IMI/REL experienced late microbiological failure associated with growth of an IMI/REL resistant pathogen (*K. pneumoniae* at 100,000 CFU/mL) after initially being infected with an IMI/REL susceptible pathogen at baseline, for which the participant received non-study gentamicin. This confirms that late failures as a result of emergent resistance were indeed infrequent in the study.

2.6.4. Conclusions on the clinical efficacy

No formal efficacy hypotheses were tested in P021; therefore, no formal efficacy conclusions can be made. Clinical efficacy of IMI/REL in the paediatric population for the sought indications is established by extrapolation from adults, where clinical efficacy and safety have previously been established in pivotal clinical studies, via exposure-matching.

2.7. Clinical safety

Introduction

Recarbrio was first approved by EMA in 2020 for use in adults for treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

The most common side effects with Recarbrio (which may affect up to 1 in 10 people) are diarrhoea and increases of hepatic enzymes. Recarbrio must not be used in patients who are hypersensitive to imipenem and other carbapenem antibiotics or in patients who have had a severe allergic reaction to beta-lactam antibiotics.

There are no important risks or missing information that require special risk management.

Patient exposure

Phase 2/3 Study (P021)

A total of 115 participants were randomised, and 113 participants received at least 1 dose of study intervention. Most randomised participants (>96%) completed the study, and most participants (>82%) completed study intervention. The most common reasons for discontinuing study intervention were "other" (7.1%) in the IMI/REL group and "adverse event" and "physician decision" (each 7.1%) in the Active Control group.

Seven participants with cUTI discontinued study intervention with a reason of "other" (ie, discontinued study intervention due to "extenuating circumstances," which included microbiological criteria not being met or receipt of prohibited non-study antibacterial agents).

Participants meeting clinical criteria for cUTI were enrolled prior to confirmation of a study-qualifying pathogen from urine culture. Once urine culture results were obtained, participants without a qualifying pathogen were discontinued from the study.

Table 18 Disposition of participants, All participants randomised

	Age Cohort 1 (12 to <18 years)				Age Cohort 2 (6 to <12 years)				Age Cohort 3 (2 to <6 years)			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	10		2		31		11		22		8	
Status for Trial												
Completed	10	(100.0)	2	(100.0)	31	(100.0)	11	(100.0)	21	(95.5)	8	(100.0)
Discontinued	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	0	(0.0)
Status for Study Medication in Trial												
Started	10		2		31		11		21		8	
Completed	9	(90.0)	1	(50.0)	27	(87.1)	9	(81.8)	19	(90.5)	7	(87.5)
Discontinued	1	(10.0)	1	(50.0)	4	(12.9)	2	(18.2)	2	(9.5)	1	(12.5)
Adverse Event	0	(0.0)	0	(0.0)	3	(9.7)	1	(9.1)	0	(0.0)	0	(0.0)
Physician Decision	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	1	(4.8)	1	(12.5)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Other[a]	1	(10.0)	0	(0.0)	1	(3.2)	1	(9.1)	1	(4.8)	0	(0.0)

	Age Cohort 4 (3 months to <2 years)				Age Cohort 5 (Birth to <3 months)				Total			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	15		5		8		3		86		29	
Status for Trial												
Completed	15	(100.0)	4	(80.0)	7	(87.5)	3	(100.0)	84	(97.7)	28	(96.6)
Discontinued	0	(0.0)	1	(20.0)	1	(12.5)	0	(0.0)	2	(2.3)	1	(3.4)
Withdrawal By Parent/Guardian	0	(0.0)	1	(20.0)	1	(12.5)	0	(0.0)	2	(2.3)	1	(3.4)
Status for Study Medication in Trial												
Started	15		4		8		3		85		28	
Completed	11	(73.3)	3	(75.0)	6	(75.0)	3	(100.0)	72	(84.7)	23	(82.1)
Discontinued	4	(26.7)	1	(25.0)	2	(25.0)	0	(0.0)	13	(15.3)	5	(17.9)
Adverse Event	1	(6.7)	1	(25.0)	0	(0.0)	0	(0.0)	4	(4.7)	2	(7.1)
Physician Decision	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.4)	2	(7.1)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(1.2)	0	(0.0)
Other[a]	2	(13.3)	0	(0.0)	1	(12.5)	0	(0.0)	6	(7.1)	1	(3.6)

[a] Includes participants with extenuating circumstances (eg., microbiological criteria not met, receipt of prohibited non-study antibiotics).

Each Participant is counted once for Status for Trial, Status for Study Medication in Trial based on the latest corresponding disposition record.

The % is based on the number of participants in the population.

Extent of exposure to study therapy (both IV and oral step-down) was generally comparable for both intervention groups in the APaT (all participants as treated) population.

IV Therapy:

All participants with HABP/VABP received IV therapy for at least 7 days; no participant received IV therapy for more than 14 days (total median duration: IMI/REL: 13.0 days [range: 7 to 14 days], Active Control: 7.0 days [range: 7 to 7 days]).

Most participants with cIAI had at least 3 days and no more than 14 days of IV therapy (total median duration: IMI/REL: 6.0 days [range: 2 to 21 days], Active Control: 8.0 days [range: 3 to 13 days]). Note: An investigator extended the duration of IMI/REL treatment to 21 days for *Actinomyces naeslundii* infection in 1 participant.

Most participants with cUTI had at least 3 days and no more than 14 days of IV therapy (total median duration: IMI/REL: 5.0 days [range: 1 to 14 days], Active Control: 5.0 days [range: <1 to 9 days]).

IV Therapy Plus Oral Step-down Therapy:

Most participants with cIAI had at least 5 days and no more than 14 days of IV plus oral step-down therapy (median duration: IMI/REL: 9.0 days [range: 2 to 21 days], Active Control: 8.5 days [range: 5 to 13 days]).

The majority of participants with cUTI had at least 5 days and no more than 14 days of IV plus oral step-down therapy (median duration: IMI/REL: 9.0 days [range: 1 to 14 days], Active Control: 7.0 days [range: 4 to 13 days]).

Demographic and other baseline characteristics were generally comparable for both intervention groups, with the exception of the proportion of participants of "Not Hispanic or Latino" ethnicity, which was lower in the IMI/REL group (58.1%) compared with the Active Control group (69.0%).

The majority of participants were White and not Hispanic or Latino. More participants with cIAI or cUTI were enrolled compared with HABP/VABP.

Most participants in the Age Cohorts 1, 2, and 3 had cIAI, whereas most participants in Age Cohorts 4 and 5 had cUTI.

Table 19 Participant Characteristics by Age Cohort

	Age Cohort 1 (12 to <18 years)				Age Cohort 2 (6 to <12 years)				Age Cohort 3 (2 to <6 years)			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	10		2		31		11		22		8	
Sex												
Male	2	(20.0)	1	(50.0)	18	(58.1)	3	(27.3)	10	(45.5)	5	(62.5)
Female	8	(80.0)	1	(50.0)	13	(41.9)	8	(72.7)	12	(54.5)	3	(37.5)
Race												
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	1	(12.5)

Asian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Black Or African American	0	(0.0)	0	(0.0)	2	(6.5)	1	(9.1)	0	(0.0)	0	(0.0)
Multiple	3	(30.0)	1	(50.0)	2	(6.5)	0	(0.0)	2	(9.1)	2	(25.0)
American Indian Or Alaska Native, White	3	(30.0)	1	(50.0)	2	(6.5)	0	(0.0)	1	(4.5)	1	(12.5)
Black Or African American, White	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(4.5)	1	(12.5)
White	7	(70.0)	1	(50.0)	27	(87.1)	10	(90.9)	19	(86.4)	4	(50.0)
Ethnicity												
Hispanic Or Latino	5	(50.0)	1	(50.0)	9	(29.0)	1	(9.1)	12	(54.5)	4	(50.0)
Not Hispanic Or Latino	5	(50.0)	1	(50.0)	21	(67.7)	10	(90.9)	10	(45.5)	4	(50.0)
Not Reported	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Infection Type												
cIAI	5	(50.0)	1	(50.0)	21	(67.7)	7	(63.6)	14	(63.6)	5	(62.5)
cUTI	4	(40.0)	1	(50.0)	10	(32.3)	4	(36.4)	6	(27.3)	2	(25.0)
HABP/VABP	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(9.1)	1	(12.5)

	Age Cohort 4 (3 months to <2 years)				Age Cohort 5 (Birth to <3 months)				Total			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	%	n	%	n	%	n	%	n	%	n	%
Participants in population	15		5		8		3		86		29	
Sex												
Male	8	(53.3)	4	(80.0)	5	(62.5)	3	(100.0)	43	(50.0)	16	(55.2)
Female	7	(46.7)	1	(20.0)	3	(37.5)	0	(0.0)	43	(50.0)	13	(44.8)
Race												
American Indian Or Alaska Native	2	(13.3)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.5)	1	(3.4)
Asian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.4)
Black Or African American	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.5)	1	(3.4)
Multiple	1	(6.7)	0	(0.0)	0	(0.0)	1	(33.3)	8	(9.3)	4	(13.8)
American Indian Or Alaska Native, White	1	(6.7)	0	(0.0)	0	(0.0)	1	(33.3)	7	(8.1)	3	(10.3)
Black Or African American, White	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.2)	1	(3.4)
White	11	(73.3)	5	(100.0)	8	(100.0)	2	(66.7)	72	(83.7)	22	(75.9)
Ethnicity												
Hispanic Or Latino	5	(33.3)	1	(20.0)	3	(37.5)	2	(66.7)	34	(39.5)	9	(31.0)
Not Hispanic Or Latino	9	(60.0)	4	(80.0)	5	(62.5)	1	(33.3)	50	(58.1)	20	(69.0)
Not Reported	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(2.3)	0	(0.0)
Infection Type												
cIAI	0	(0.0)	1	(20.0)	0	(0.0)	0	(0.0)	40	(46.5)	14	(48.3)
cUTI	14	(93.3)	4	(80.0)	7	(87.5)	3	(100.0)	41	(47.7)	14	(48.3)
HABP/VABP	1	(6.7)	0	(0.0)	1	(12.5)	0	(0.0)	5	(5.8)	1	(3.4)

cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated Urinary Tract Infection; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-associated bacterial pneumonia.

Phase 1b Study (P020)

Forty-seven participants were allocated across Cohorts 1 through 5; 46 (97.9%) were treated, and all treated participants completed the study. A total of 46 treated participants received a single IV dose of IMI/REL. The majority of participants were female (59.6%), White (78.7%), and of non-Hispanic or Latino (83.0%) ethnicity.

Adverse events

Phase 2/3 Study (P021)

Overall, 71 (62.8%) participants experienced at least 1 AE. There was a higher observed percentage of participants who experienced at least 1 AE in the IMI/REL group (67.1%) compared with the Active Control group (50.0%); however, the 95% CIs for the difference in percentage for IMI/REL versus Active Control included 0.

The percentage of participants who had any drug-related AE, SAE, and AE leading to discontinuation was comparable for both intervention groups. Most AEs were considered by the investigator to be not related to the study intervention. There were no AEs with an outcome of death or SAEs leading to discontinuations of IV study intervention. Few participants had drug-related SAEs, AEs leading to discontinuations of IV study intervention, or discontinuations due to drug-related AEs.

The percentage of participants with AEs was generally comparable for both intervention groups for each infection type and within each age cohort. Limited interpretation can be made on the differences observed in the percentages of participants who had AEs across age cohorts due to the small sample size.

Table 20 Analysis of Adverse Event Summary During Therapy and 14-Day Follow-Up Period, All Participants as Treated

	IMI/REL		Active Control		Difference in % vs Active Control
	n	(%)	n	(%)	Estimate (95% CI)[c]
Participants in population	85		28		
with one or more adverse events	57	(67.1)	14	(50.0)	17.1 (-3.5, 37.2)
with no adverse event	28	(32.9)	14	(50.0)	-17.1 (-37.2, 3.5)
with drug-related[a] adverse events	17	(20.0)	5	(17.9)	2.1 (-17.2, 16.6)
from IV therapy	16	(18.8)	5	(17.9)	1.0 (-18.3, 15.3)
from oral step-down therapy	1	(1.2)	0	(0.0)	1.2
with serious adverse events	10	(11.8)	3	(10.7)	1.1 (-16.4, 12.5)
with serious drug-related[a] adverse events	2	(2.4)	0	(0.0)	2.4
from IV therapy	1	(1.2)	0	(0.0)	1.2
from oral step-down therapy	1	(1.2)	0	(0.0)	1.2
who died	0	(0.0)	0	(0.0)	0.0
discontinued drug due to an adverse event[d]	5	(5.9)	2	(7.1)	-1.3 (-17.3, 7.8)
discontinued IV therapy[b]	3	(3.5)	0	(0.0)	3.5
discontinued oral step-down therapy	2	(2.4)	2	(7.1)	-4.8 (-20.6, 2.8)
discontinued drug due to a drug-related adverse event[d]	3	(3.5)	0	(0.0)	3.5
discontinued IV therapy[b]	2	(2.4)	0	(0.0)	2.4
discontinued oral step-down therapy	1	(1.2)	0	(0.0)	1.2

	IMI/REL		Active Control		Difference in % vs Active Control
	n	(%)	n	(%)	Estimate (95% CI)[c]
discontinued drug due to a serious adverse event[d]	2	(2.4)	2	(7.1)	-4.8 (-20.6, 2.8)
discontinued IV therapy[b]	0	(0.0)	0	(0.0)	0.0
discontinued oral step-down therapy	2	(2.4)	2	(7.1)	-4.8 (-20.6, 2.8)
discontinued drug due to a serious drug-related adverse event[d]	1	(1.2)	0	(0.0)	1.2
discontinued IV therapy[b]	0	(0.0)	0	(0.0)	0.0
discontinued oral step-down therapy	1	(1.2)	0	(0.0)	1.2

[a] Determined by the investigator to be related to the drug.

[b] IV study medication withdrawn during IV treatment phase.

[c] Based on Miettinen & Nurminen method, and presented if incidence ≥12 participants in the IMI/REL group or ≥2 participants in the Active Control group.

[d] One participant in the IMI/REL arm discontinued oral step-down therapy due to an AE, however, the participant did not require subsequent antibiotic therapy and hence their status for study medication in trial was reported as completed.

The most frequently reported AEs (incidence ≥5% in either intervention group) in the IMI/REL group were vomiting (15.3%), diarrhoea (9.4%), nausea (7.1%), abdominal pain (5.9%), headache (5.9%), pyrexia (5.9%), and thrombocytosis (5.9%). The most frequently reported AEs in the Active Control group were vomiting (10.7%), diarrhoea (7.1%), nasopharyngitis (7.1%), nausea (7.1%), pyrexia (7.1%), and tachycardia (7.1%).

Adverse Events Related to Study Intervention

Drug-related Adverse Events (IV or Oral Step-down):

Overall, 22 (19.5%) participants had drug-related AEs, which were generally comparable for both intervention groups (IMI/REL: 20.0%; Active Control: 17.9%).

The most frequently reported drug-related AEs (incidence ≥2% in either intervention group) were nausea (3.5%), vomiting (3.5%), chromaturia (2.4%), and pruritus (2.4%) in the IMI/REL group and diarrhea (7.1%), nausea (7.1%), abdominal pain (3.6%), infusion site phlebitis (3.6%), and vomiting (3.6%) in the Active Control group.

Drug-related Adverse Events (IV Only):

The percentage of participants who had AEs related to IV therapy was generally comparable for both intervention groups (IMI/REL: 18.8%; Active Control: 17.9%).

Drug-related Adverse Events (Oral Step-down Only):

One participant in the IMI/REL group had an AE related to oral step-down therapy (drug intolerance). This AE was reported as an SAE and is presented in detail below.

Adverse Events by Maximum Intensity

Most participants had AEs that were mild or moderate in intensity and generally comparable for both intervention groups.

The percentage of participants who had severe AEs was generally comparable for both intervention groups (IMI/REL: 10.6%; Active Control: 10.7%). Except for urinary tract infection reported for 2 (2.4%) participants in the IMI/REL group, the remaining severe AEs were reported for 1 participant in either intervention group.

Serious adverse event/deaths/other significant events

All Serious Adverse Events

The percentage of participants with SAEs was comparable for both intervention groups (IMI/REL: 11.8%; Active Control: 10.7%). Of the SAEs that were reported, most were reported for 1 participant in either intervention group (IMI/REL: calculus urinary, drug intolerance, Escherichia urinary tract infection, food poisoning, and short bowel syndrome; Active Control: gastroenteritis rotavirus, neonatal infection, and postoperative wound infection). The exceptions were intestinal obstruction reported for 2 (2.4%) participants and urinary tract infection reported for 3 (3.5%) participants in the IMI/REL group. All of the SAEs were resolved.

No participants had an SAE leading to discontinuation of IV study intervention. Two participants in each intervention group (IMI/REL: 2.4%; Active Control: 7.1%) had an SAE leading to discontinuation of study intervention during oral step-down therapy.

Table 21 Participants With Serious Adverse Events During Therapy and 14-Day Follow-Up Period by Age Cohort , (Incidence > 0% in Any Column), All Participants as Treated

	Age Cohort 1 (12 to <18 years)		Age Cohort 2 (6 to <12 years)		Age Cohort 3 (2 to <6 years)	
	IMI/REL	Active Control	IMI/REL	Active Control	IMI/REL	Active Control
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Participants in population	10	2	31	11	21	8
with one or more serious adverse events	0 (0.0)	0 (0.0)	6 (19.4)	1 (9.1)	0 (0.0)	0 (0.0)
with no serious adverse events	10 (100.0)	2 (100.0)	25 (80.6)	10 (90.9)	21 (100.0)	8 (100.0)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**3 (9.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Food poisoning	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal obstruction	0 (0.0)	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
Short-bowel	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

	Age Cohort 1 (12 to <18 years)				Age Cohort 2 (6 to <12 years)				Age Cohort 3 (2 to <6 years)			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
syndrome												
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Drug intolerance	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.2)**	**1**	**(9.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Escherichia urinary tract infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastroenteritis rotavirus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neonatal infection	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Postoperative wound infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(9.1)	0	(0.0)	0	(0.0)
Urinary tract infection	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Calculus urinary	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	0	(0.0)	0	(0.0)

	Age Cohort 4 (3 months to <2 years)				Age Cohort 5 (Birth to <3 months)				Total			
	IMI/REL		Active Control		IMI/REL		Active Control		IMI/REL		Active Control	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	15		4		8		3		85		28	
with one or more serious adverse events	4	(26.7)	1	(25.0)	0	(0.0)	1	(33.3)	10	(11.8)	3	(10.7)
with no serious adverse events	11	(73.3)	3	(75.0)	8	(100.0)	2	(66.7)	75	(88.2)	25	(89.3)

	Age Cohort 4 (3 months to <2 years)		Age Cohort 5 (Birth to <3 months)		Total	
	IMI/REL	Active Control	IMI/REL	Active Control	IMI/REL	Active Control
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	**1 (6.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**4 (4.7)**	**0 (0.0)**
Food poisoning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)
Short-bowel syndrome	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.2)**	**0 (0.0)**
Drug intolerance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Infections and infestations	**3 (20.0)**	**1 (25.0)**	**0 (0.0)**	**1 (33.3)**	**4 (4.7)**	**3 (10.7)**
Escherichia urinary tract infection	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Gastroenteritis rotavirus	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Neonatal infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (3.6)
Postoperative wound infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Urinary tract infection	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.5)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.2)**	**0 (0.0)**
Calculus urinary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)

Every participant is counted a single time for each applicable row and column.

Study Intervention–related Serious Adverse Events

Two participants, both in the IMI/REL group (1 with calculus urinary and 1 with drug intolerance), had SAEs that were considered by the investigator to be drug related. Of these, the SAE of calculus urinary was considered by the investigator to be related to IV therapy. Study intervention continued with no modification, and the SAE was resolved after a duration of 5 days. The SAE of drug intolerance was

considered by the investigator to be related to oral step-down therapy. Oral step-down therapy was discontinued, and IV therapy resumed. The drug intolerance was resolved 23 hours after its onset.

Deaths

There were no deaths reported during this study.

Other Significant Adverse Events

Adverse Events Leading to Discontinuation of Study Intervention

AEs leading to discontinuation of study intervention were reported for 5 (5.9%) participants in the IMI/REL group and 2 (7.1%) participants in the Active Control group. All of these AEs resolved during the study.

AEs leading to discontinuation of IV study intervention were reported for 3 (3.5%) participants in the IMI/REL group (peripheral swelling, rash, and rash erythematous) and none in the Active Control group. Of these, the AEs of rash and rash erythematous were considered by the investigator to be related to IV study intervention.

Events of Clinical Interest

Elevated liver enzymes or potential drug-induced liver injury events meeting specific criteria were predefined in the protocol as ECIs.

No ECIs were reported in the study.

Phase 1b Study (P020)

For Cohorts 1 to 5, 8 (17.4%) participants experienced at least 1 AE. Of these participants, 7 had AEs that were mild in intensity, and 1 participant in Cohort 3 had an AE categorised by the investigator as severe in intensity. All reported AEs occurred in the posttreatment period, and none led to infusion interruption/discontinuation or study discontinuation. No AEs were reported for participants in Cohort 2 and in Subcohorts 2 and 3 of Cohort 5. 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 anaemia (6.5%) and diarrhoea (6.5%).

Two (4.3%) participants (1 in Cohort 1 and 1 in Cohort 3) had a total of 4 AEs assessed by the investigator to be drug related (increased ALT, increased AST, anaemia, and diarrhoea). These events were nonserious, mild in severity, and resolved for both participants by the end of the study.

No protocol predefined ECI of elevations in liver transaminases was reported during the study.

Table 22 Adverse Event Summary, During IV Therapy and 14-Day Follow-Up Period, Safety Population

	Cohort 1 (15/7.5 mg/kg)		Cohort 2 (15/7.5 mg/kg)		Cohort 3 (15/7.5 mg/kg)		Cohort 4 (10/5 mg/kg)		Cohort 4 (15/7.5 mg/kg)		Cohort 5 Subcohort 1 (10/5 mg/kg)		Cohort 5 Subcohort 2 (10/5 mg/kg)		Cohort 5 Subcohort 3 (10/5 mg/kg)		Cohort 5 Subcohort 1 (15/7.5 mg/kg)		Cohort 5 Subcohort 2 (15/7.5 mg/kg)		Cohort 5 Subcohort 3 (15/7.5 mg/kg)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	7		6		6		4		4		5		3		2		2		3		4		46	
with one or more adverse events	1	(14.3)	0	(0.0)	3	(50.0)	1	(25.0)	2	(50.0)	1	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	8	(17.4)
with no adverse event	6	(85.7)	6	(100.0)	3	(50.0)	3	(75.0)	2	(50.0)	4	(80.0)	3	(100.0)	2	(100.0)	2	(100.0)	3	(100.0)	4	(100.0)	38	(82.6)
with drug-related[a] adverse events	1	(14.3)	0	(0.0)	1	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(4.3)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

The initial dose for Cohort 1 is 15/7.5 mg/kg prior to interim review, all subjects received the full adult dose of 500/250 mg IMI/REL based on their weight. Therefore, the dose was modified to 500/250 mg after the interim review.

MedDRA version 23.0.

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 subcohort 1=4 weeks to <3 months; Cohort 5 subcohort 2=1 to <4 weeks; Cohort 5 subcohort 3=<1 week

Laboratory findings

Phase 2/3 Study (P021)

The percentage of participants with postbaseline Grade 1 to 3 (none reported for Grade 4) increases in laboratory abnormalities during treatment and through the 14-day follow-up period was generally comparable for both intervention groups

Phase 1b Study (P020)

In general, no clinically meaningful changes in chemistry and haematology mean values were observed in any of the cohorts from baseline to Visit 3.

Thirty-eight participants had at least 1 laboratory value at posttreatment Visit 3 that met DMID or DAIDS toxicity grades of 1 to 4. The majority had DMID Grade 1 or DMID Grade 2 laboratory toxicities.

None of the DMID Grade 1 to 4 laboratory toxicities led to discontinuation from the study.

Vital signs, physical findings, and other observations related to safety

Phase 2/3 Study (P021)

Abnormalities in vital signs and physical examinations reported as AEs are listed in adverse events section. None of these AEs were serious or led to discontinuation of study intervention.

Phase 1b Study (P020)

No clinically meaningful changes in vital sign mean values were observed in any of the age cohorts.

Safety in special populations

Intrinsic Factors

Evaluation of the safety of IMI/REL by age was performed. Other intrinsic factors (eg, gender, body weight, ethnicity, hepatic impairment, and renal impairment) were not assessed. Participant disposition did not support evaluation of the safety of IMI/REL by renal function.

Phase 2/3 Study (P021)

The percentage of participants with AEs was generally comparable for both intervention groups within each age cohort. Limited interpretation can be made on the differences observed in the percentages of participants who had AEs across age cohorts due to the small sample size.

Phase 1b Study (P020)

The AE profile was generally comparable between Cohorts 1 to 3 and Cohorts 4 and 5, indicating no clinically meaningful difference associated with age in safety profile.

Extrinsic Factors

Evaluations of the safety of IMI/REL by extrinsic factors were not performed for P020 or P021.

Safety related to drug-drug interactions and other interactions

DDIs were not evaluated in P021 or P020. No new DDI studies were conducted for the paediatric indication. Information about the evaluation of DDIs for IMI/REL was provided in the original application for the adult indications.

Discontinuation due to adverse events

One participant in IMI/REL Cohort 4 during i.v. therapy. One participant in IMI/REL group discontinued due to SAE during oral step-down.

Post marketing experience

IMI/REL has been registered and approved for use in adults in >50 countries. IMI/REL was first approved in the US on 16-JUL-2019 for the treatment of cUTI, including pyelonephritis and cIAI, in patients with limited or no alternative treatment options. A supplemental new drug application for treatment of HABP and VABP was approved in the US on 04 Jun 2020.

IMI/REL was approved in the EU on 13 Feb 2020 for treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options. A variation application for extending the marketing authorisation with the indications for treatment of HABP and VABP in adults and treatment of bacteraemia that occurs in association with, or is suspected to be associated with, HABP and VABP in adults was approved in the EU on 16 Nov 2020.

To date, there have been no regulatory or manufacturer actions related to IMI/REL due to safety reasons.

Cumulative post-marketing patient exposure estimates for IMI/REL were calculated from the MAH's internal distribution data from the FSA database. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. Cumulatively to 15 Jul 2024, approximately 16,147 patients have received IMI/REL.

The company's safety database was queried for valid, spontaneous, and noninterventional study reports of IMI/REL cumulatively to 15 Oct 2024. Summary tabulations of the serious and nonserious AEs from post-marketing sources include reports from health care providers, consumers, and scientific literature, as well as from competent authorities worldwide.

Results:

Post-marketing data available through 15 Oct 2024 are summarised below to provide overall context for the current known benefit-risk profile for IMI/REL. As a case may contain events in more than 1 SOC, the total number of events may be greater than the total number of reports.

As of 15 Oct 2024, there were 161 AE reports containing 372 events. Of the 372 events, 123 were considered serious, and 249 were nonserious. The SOCs with the highest number of AEs were Injury, poisoning and procedural complications; General disorders and administration site conditions; and Infections and infestations.

- The Injury, poisoning and procedural complications SOC contained 127 events; 4 were considered serious, and 123 were nonserious. The 3 most common PTs in this SOC were product use in unapproved indication (n=54 events), off-label use (n=24 events), and underdose (n=9 events).
- The General disorders and administration site conditions SOC contained 93 events; 25 were considered serious, and 68 were nonserious. The 3 most common PTs in this SOC were no AE (n=32 events), drug ineffective (n=19 events), and death (n=15 events).
- The Infections and infestations SOC contained 47 events; 36 were considered serious, and 11 were nonserious. The most common PTs in this SOC were pathogen resistance (n=10 events), sepsis (n=6 events), bacteraemia (n=3 events), infection (n=3 events), and pneumonia (n=3 events).

Of the 161 post-marketing reports of IMI/REL in the company's global safety database cumulative to 15 Oct 2024, 1 case contained a reported patient age of less than 18 years. This case report describes 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.

A tabular summary of serious and nonserious event count in adults by SOC for the 161 post-marketing reports is presented below.

Table 23 MK-7655A Adverse Event Count by System Organ Class Cumulative to 15-OCT-2024

Event System Organ Class	Nonserious (Event Count)	Serious (Event Count)
Blood and lymphatic system disorders	0	4
Cardiac disorders	0	4
Gastrointestinal disorders	7	0
General disorders and administration site conditions	68	25
Hepatobiliary disorders	1	2
Immune system disorders	0	2
Infections and infestations	11	36
Injury, poisoning and procedural complications	123	4
Investigations	22	3
Metabolism and nutrition disorders	0	2
Musculoskeletal and connective tissue disorders	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3
Nervous system disorders	1	16
Product issues	3	0
Renal and urinary disorders	0	5
Respiratory, thoracic and mediastinal disorders	4	8
Skin and subcutaneous tissue disorders	2	1
Surgical and medical procedures	6	7
Vascular disorders	0	1
Total	249	123

The 3 SOCs in which SAEs were most frequently reported were: Infections and infestations (36 SAEs), General disorders and administration site conditions (25 SAEs), and Nervous system disorders (16 SAEs). Of the 123 SAEs, none were reported for patients less than 18 years of age.

- The Infections and infestations SOC contained 36 SAEs. The most common PTs in this SOC were pathogen resistance and sepsis (n=6 SAEs each), bacteraemia and pneumonia (n=3 SAEs each), and pneumonia pseudomonal and septic shock (n=2 SAEs each).

    - The identified reports with SAEs under this Infections and infestations SOC either contain insufficient information to assess or are confounded by underlying conditions, concomitant disease states, concurrent treatments, and/or a lack of temporal relationship. The overall number, type, and frequency of SAEs reported were representative of participants with the indicated infections and do not suggest any new safety concerns for IMI/REL. The information provided in these reports does not suggest a causal relationship between IMI/REL and the reported events.

- The General disorders and administration site conditions SOC contained 25 SAEs. The most common PTs in this SOC were death (n=15 SAEs) and drug ineffective and ill-defined disorder (n=2 SAEs each).
    - Of the 15 cases with the PT of death, age was reported in 8 cases, 4 of which were patients ≥75 years. Sepsis, septic shock, and urosepsis were reported as concurrent conditions in 6 of the 15 cases. The remaining cases described patients who either have multiple comorbidities (i.e., malignancies, cardiac arrest, and pseudomonal infections or pneumonia) or who were in poor general health. No notable or unanticipated safety signals of concern were identified.
- The Nervous system disorders SOC contained 16 SAEs. The most common PTs in this SOC were epilepsy (n=4 SAEs), seizure (n=3 SAEs), and depressed level of consciousness and encephalopathy (n=2 SAEs each).

The assessment of SAEs in the company's safety database did not identify any new safety concerns. The SAEs were generally consistent with manifestations or complications of the patient's underlying disease, reflecting the critically ill nature of patients who receive IMI/REL, were consistent with the known safety profile of the drug, had limited information, or contained confounding information.

The following are the important identified/potential risks for IMI/REL:

- Important Identified Risks
    - Hypersensitivity reactions
    - Increased seizure potential due to interaction with valproic acid or divalproex sodium
    - *Clostridioides difficile*–associated diarrhoea
    - CNS adverse experiences such as seizures, confusional states, and myoclonic activity have been reported during treatment with imipenem/cilastatin, a component of IMI/REL, especially when recommended dosages of imipenem were exceeded. CNS events, including seizures and confusional states, have been reported in clinical trials with IMI/REL. The majority of these events were either not considered to be drug-related or did not require treatment discontinuation.
- There are no Important Potential Risks

The cumulative analysis of this post-marketing safety data reviewed did not change the risk profile of IMI/REL.

Additionally, there were no published or available draft manuscripts or abstracts that described new and potentially important safety information, no new safety concerns have been identified.

Analysis of the post-marketing data supports the adequacy of the current Company Core Safety Information for IMI/REL in terms of product safety and the adequacy of the current pharmacovigilance plan and risk minimisation plan for the safety concerns. Analysis of the post-marketing data also

supports the adequacy of the current Core Risk Management Plan for IMI/REL. As with all MAH products, the safety profile of IMI/REL is closely monitored on a continuing basis.

2.7.1. Discussion on clinical safety

Out of the 85 participants receiving IMI/REL treatment, 51 (67.1%) reported at least one adverse event. Of these, 17 (20%) were considered related to treatment by the investigator. Most common drug-related adverse events (incidence ≥2%) were nausea, vomiting, chromaturia, and pruritus. Most events were of mild intensity and comparable between intervention and control groups. One serious drug-related adverse event of urinary calculus was reported; the event resolved within 5 days without modification of study treatment. No deaths were reported. In the IMI/REL groups, 5 participants discontinued therapy due to adverse events, 3 of which (peripheral swelling, rash, and rash erythematous) occurred during i.v. therapy. No AESIs were reported.

Given the long experience of imipenem use and it's known safety profile, it is reasonable to extrapolate the information from these experiences, and consequently, an update of section 4.4 of SmPC is made to state that '*Special awareness should be made to neurological symptoms or convulsions in children with known risk factors for seizures, or on concomitant treatment with medicinal products lowering the seizures threshold*'.

2.7.2. Conclusions on clinical safety

Data from the clinical paediatric program adds information on safety of IMI/REL from 85 paediatric patients. While data is limited, no new safety information was identified in the review of reports adverse events or scientific literature. No deaths were reported. No new safety concerns were identified based on the submitted data.

2.7.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European Medicines Agency web-portal.

2.8. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

This RMP has been updated to cover new indication of imipenem/cilastatin/relebactam for treatment in the paediatric population (birth to less than 18 years of age) with confirmed or suspected gram-negative bacterial infections.

Final study data following the completion of MK-7655A Study P021, a Phase 2/3 Open-label, Randomized, Active-controlled Clinical Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of MK-7655A in Paediatric Participants From Birth to Less Than 18 Years of Age With Confirmed or Suspected Gram-negative Bacterial Infection, have been included.

Summary of significant changes in this RMP:

RMP Section	UPDATED INFORMATION
DATA LOCK POINT	Updated to 30-NOV-2024 to reflect the most recent available post-marketing exposure data.
PART I: PRODUCT(S) OVERVIEW	Updated proposed additional indications
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	Added updated information regarding incidence of confirmed or suspected gram-negative bacterial infections in the pediatric population, from birth to less than 18 years of age.
PART II: MODULE SII-NON-CLINICAL PART OF SAFETY SPECIFICATION	Added the juvenile animal study data for imipenem/cilastatin/relebactam
PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE	Removed table of Phase 1 exposure data to focus on pivotal trial data Updated exposure tables to present aggregated data versus by individual trials Added clinical trial patient exposure data from Study P021 throughout
PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS	Added exclusion criteria from Study P021.
PART II: MODULE SV – POST-AUTHORIZATION EXPERIENCE	Updated statement regarding marketing approval. Added exposure tables to present cumulative post-authorization exposure since market introduction.
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT	Updated “I. The Medicine and What it is Used For”

There have been no changes to the list of safety concerns for imipenem/cilastatin/relebactam with this RMP update. There continues to be no important identified risks, important potential risks, or missing information for the product.

PRAC assessment of the relevant parts of the RMP

1.Safety Specification

Having considered the data in the safety specification the PRAC Rapporteur agrees that the safety specification proposed by the MAH is appropriate.

2.Part III Pharmacovigilance plan

The PRAC Rapporteur having considered the data submitted, is of the opinion that: routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

3.Part IV Plans for post-authorisation efficacy studies

Not applicable. There are no ongoing or proposed post-authorisation efficacy studies (PAES) for IMI/REL.

4.Part V Risk minimisation measures

There is no safety concern identified for IMI/REL as described in Part II Module SVII Summary of the Safety Concerns of this Risk Management Plan.

5.Part VI Summary of activities in the risk management plan by medicinal product

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

2.9. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and implement editorial corrections.

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet, based on the absence of significant changes, has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Multi-drug resistant (MDR) gram-negative bacterial infections are difficult to treat and are associated with longer hospital stays in paediatric patients.

HABP/VABP remains a cause of significant morbidity and mortality amongst paediatric patients, including neonates. cIAI is also a common paediatric condition, most often secondary to appendicitis. UTIs are amongst the most commonly diagnosed infections in children and complicated UTIs are associated with protracted clinical course, drug resistant pathogens and higher morbidity and mortality.

3.1.2. Available therapies and unmet medical need

Treatment of Gram-negative infections in paediatric patients includes consideration of such factors as the site and severity of infection and recent prior antibacterial use. Empiric therapy should be sufficiently broad spectrum so as to cover anticipated pathogens and locally observed resistance profiles. Targeted therapy should be given once urine culture and susceptibility results are available.

Despite the availability of multiple antibiotics for use in the treatment of HABP/VABP, cIAI, and cUTI, in paediatric patients, the emergence and global spread of resistant pathogens have created an unmet medical need for safe and effective alternative agents. Few broad-spectrum antibacterial agents are formally approved for use in paediatric patients.

3.1.3. Main clinical studies

Study P021 was a Phase 2/3 open-label, randomised, SOC-controlled study of safety, tolerability, efficacy and pharmacokinetics of IMI/REL versus locally determined (not protocol-defined) SOC in 115 paediatric participants from birth to <18 years with confirmed or suspected Gram-negative bacterial infections including cUTI, cIAI and HABP/VABP. The primary objectives were safety and PK, and efficacy endpoints were only secondary. The study was not powered for inferential analyses.

The main secondary efficacy endpoints were protocol-defined favourable clinical outcome and favourable microbiological outcome at EOT, EFU and LFU visits. The populations used for descriptive efficacy analyses were MITT an mMITT.

Most randomised participants had cUTI or cIAI, with HABP/VABP comprising a minority of participants (IMI/REL: 5 [5.8%]; Active Control: 1 [3.4%]), which is perhaps not surprising. The most common baseline pathogens from infection site cultures in the IMI/REL group (>5% of participants) were Escherichia coli (48 participants [70.6%]), Pseudomonas aeruginosa (12 [17.6%]), Klebsiella pneumoniae (4 [5.9%]), and Bacteroides fragilis (4 [5.9%]) and similar in the Active control group. Of the baseline qualifying pathogens from primary site isolates in the mMITT population, susceptibility (according to EUCAST breakpoint 2mg/L) to imipenem/REL was generally comparable for the IMI/REL (76.3% of pathogens) and Active Control (71.0%) groups.

3.2. Favourable effects

Clinical efficacy of IMI/REL in the paediatric population for the sought indications is established by extrapolation from adults, where clinical efficacy and safety have previously been established in pivotal clinical studies, via exposure-matching.

Descriptive results showed that the rate of favourable clinical response and favourable microbiological response was high (>69% in both intervention groups and >85% in both intervention groups, respectively) across EOT, EFU and LFU visits in both the MITT and mMITT populations, and numerically similar between IMI/REL and Active comparator arms. No participants died in either intervention group in the study through Day 28.

3.3. Uncertainties and limitations about favourable effects

No formal efficacy hypotheses were tested in study P021; therefore, no formal efficacy conclusions can be made on the basis of the efficacy data alone. Clinical efficacy of IMI/REL in the paediatric population for the sought indications is however established by extrapolation from adults.

3.4. Unfavourable effects

Of the 85 participants receiving IMI/REL treatment, 51 (67.1%) reported at least one adverse event. Of these, 17 (20%) were considered related to treatment by the investigator. Most common drug-related adverse events (incidence ≥2%) were nausea, vomiting, chromaturia, and pruritus. Most events were of mild intensity and comparable between intervention and control groups. One serious drug-related adverse event of urinary calculus was reported.

No deaths were reported. In the IMI/REL groups, 5 participants discontinued therapy due to adverse events, 3 of which (peripheral swelling, rash, and rash erythematous) occurred during i.v. therapy. No AESIs were reported.

3.5. Uncertainties and limitations about unfavourable effects

The clinical paediatric program is relatively limited, collecting data from 85 paediatric patients. While data is limited, no new safety information was identified in the review of reports adverse events or scientific literature.

3.6. Effects Table

Table 24 Effects Table for IMI/REL in cUTI, cIAI, HABP/VABP in paediatric patients

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
All-cause mortality D28.		%	0	0	Secondary EP. Descriptive statistics.	Study 021 CSR P021MK7655A 11.1 Efficacy results.
Favourable clinical response EOT EFU LFU	Protocol-defined. MITT population.	% (95% CI)	 78.8 (68.9, 86.2) 70.1 (60.1, 79.3) 69.4 (58.9, 78.2)	 75.0 (56.4, 87.6) 75.0 (56.4, 87.6) 75.0 (56.4, 87.6)	Secondary EP. Descriptive statistics.	
Favourable microbiological response EOT EFU LFU	Protocol-defined. mMITT population.	%(95 %CI)	 95.6 (87.3, 99.0) 85.3 (74.8, 92.0) 86.8 (76.5, 93.1)	 90.9 (71.0, 98.7) 90.9 (71.0, 98.7) 86.4 (65.8, 96.1)	Secondary EP. Descriptive statistics.	
Unfavourable Effects						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Nausea	IMI/REL group	%	3.5%	SmPC: Common		
Vomiting	IMI/REL group	%	3.5%	SmPC: Common		
Chromaturia	IMI/REL group	%	2.4%	SmPC: Rare		
Pruritus	IMI/REL group	%	2.4%	SmPC: Uncommon		

Abbreviations: CI = confidence interval; EFU = early follow-up; EOT = end of therapy; EP = endpoint; LFU = late follow-up; MITT = modified intention-to-treat; mMITT = microbiologically-evaluable modified intention-to-treat.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The need for new antibiotic options for use in paediatric patients, in particular broad-spectrum antibacterial agents active against MDR pathogens, remains high. Relebactam is a non-β-lactam BLI of the diazobicyclooctane family and an inhibitor of Ambler class A and class C β-lactamases. REL can restore the activity of imipenem against imipenem-resistant gram-negative bacteria as well as reduces the imipenem MIC in imipenem-susceptible organisms, thus providing a potentially clinically valuable option in terms of treatment of such infections.

The clinical efficacy and safety of IMI/REL has previously been established in pivotal clinical studies with adult participants. This extension of indication application to include the paediatric population from birth for the treatment of HABP/VABP and treatment of infections due to aerobic Gram-negative organisms where there are limited treatment options relies on extrapolation of clinical efficacy and safety via exposure matching. This is supported by EMA guidance (EMEA/CHMP/EWP/147013/2004) and regulatory precedent.

To this end, PK data and resulting analyses are pivotal to this submission. The popPK models for imipenem for relebactam are both tentatively considered adequate. The popPK dataset include children down to birth and an indication from birth can be supported.

The dosing is supported both by similar exposure of IMI and REL compared to adults as well as probability of target attainment simulations. The infusion time have been increased (60 minutes compared to 30 minutes) in children compared to adults to avoid excessive C_{max} values. Overall, the proposed dosing in children with normal renal function is supported.

For children weighing at least 30 kg, the same dose adjustments as in adults is proposed regarding RI and this is supported. For children below 30 kg, no recommendation regarding RI have been provided in the SmPC, which is accepted.

Overall, extrapolation from adults to children, supported by similar exposure in adults and children as well as PTA simulations is endorsed.

The descriptive efficacy data observed in the Phase 2/3 Study 021 have their limitations but generally indicate favourable clinical and microbiological outcomes that are numerically similar to locally determined active comparator (SOC).

Within this application, whilst acknowledging the very limited size of the new safety dataset, no new ADRs for IMI/REL have been identified in paediatric subjects and the reported AEs are in line with the ones that are known from studies in adult subjects.

3.7.2. Balance of benefits and risks

The clinical benefits of Recarbrio treatment are considered to outweigh the anticipated risks.

3.8. Conclusions

The overall benefit-risk of Recarbrio is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to extend the approved adult indications for RECARBRIO to include treatment of paediatric population from birth to <18 years of age, based on final results from two paediatric studies (MK-7655A-021 and MK-7655A-020); phase 2/3 study MK-7655A-021 addressed safety, tolerability, efficacy and PK, and phase 1b study MK-7655A-020 addressed PK, safety, and tolerability of MK-7655A in paediatric subjects from birth to less than 18 years of age with confirmed or suspected gram-negative infections. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and implement minor editorial corrections.

The variation leads to amendments to annexes I and IIIB, and to the Risk Management Plan (RMP).

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0190/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0190/2024 have been completed after the entry into force of that Regulation.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Recarbrio EMEA/H/C/004808 - VR/0000265089'.