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Pharmacokinetics, Safety, and Tolerability of Imipenem/Cilastatin/Relebactam in Children with Confirmed or Suspected Gram-Negative Bacterial Infections: A Phase 1b, Open-Label, Single-Dose Clinical Trial

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Abstract

Imipenem/cilastatin/relebactam is approved for the treatment of serious gram-negative bacterial infections in adults. This study assessed the pharmacokinetics (PK), safety, and tolerability of a single dose of imipenem/cilastatin/relebactam (with a fixed 2:1 ratio of imipenem/cilastatin to relebactam, and with a maximum dose of 15 mg/kg imipenem and 15 mg/kg cilastatin [≤500 mg imipenem and ≤500 mg cilastatin] and 7.5 mg/kg relebactam [≤250 mg relebactam]) in children with confirmed/suspected gram-negative bacterial infections receiving standard-of-care antibacterial therapy. In this phase 1, noncomparative study (ClinicalTrials.gov identifier, NCT03230916), PK parameters from 46 children were analyzed using both population modeling and noncompartmental analysis. The PK/pharmacodynamic (PD) target for imipenem was percent time of the dosing interval that unbound plasma concentration exceeded the minimum inhibitory concentration (%fT>MIC) of ≥30% (MIC = 2 mcg/mL). For relebactam, the PK/PD target was a free drug area under the plasma concentration–time curve (AUC) normalized to MIC (at 2 mcg/mL) of ≥8.0 (equivalent to an AUC from time zero extrapolated to infinity of ≥20.52 mcg·h/mL). Safety was assessed up to 14 days after drug infusion. For imipenem, the ranges for the geometric mean %fT>MIC and maximum concentration (C_{max}) across age cohorts were 56.5%-93.7% and 32.2-38.2 mcg/mL, respectively. For relebactam, the ranges of the geometric mean C_{max} and AUC from 0 to 6 hours across age cohorts were 16.9-21.3 mcg/mL and 26.1-55.3 mcg·h/mL, respectively. In total, 8/46 (17%) children experienced ≥1 adverse events (AEs) and 2/46 (4%) children experienced nonserious AEs that were deemed drug related by the investigator. Imipenem and relebactam exceeded plasma PK/PD targets; single doses of imipenem/cilastatin/relebactam were well tolerated with no significant safety concerns identified. These results informed imipenem/cilastatin/relebactam dose selection for further pediatric clinical evaluation.

Keywords

carbapenem/β-lactamase inhibitor, children, dose selection, gram-negative bacterial infection, imipenem/cilastatin/relebactam

As with adults, children with infections caused by extended-spectrum β-lactamase—producing pathogens and carbapenem-resistant pathogens endure longer hospital stays[1] and high rates of mortality.[2,3] Over the past 2 decades, the prevalence of multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant Enterobacterales has increased in both adults and children.[4–7] Therefore, there is an urgent need to

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investigate new therapies to treat infections caused by multidrug-resistant pathogens in children.

Based on the results of 2 pivotal phase 3 clinical trials in adults, imipenem/cilastatin/relebactam, a carbapenem/β-lactamase inhibitor combination, is currently approved for the treatment of hospital-acquired/ventilator-associated bacterial pneumonia, complicated urinary tract infection, and complicated intra-abdominal infection in adults.[8–10] Recent surveillance studies of intra-abdominal, urinary tract, and lower respiratory tract infections that together comprise adult and pediatric isolates from more than 50 countries have shown that imipenem/relebactam susceptibility rates were >90% among *P. aeruginosa* isolates, including approximately 70%-80% for multidrug-resistant *P. aeruginosa* isolates, and >97% for Enterobacterales isolates, including >96% for carbapenemase-producing *Klebsiella pneumoniae* isolates.[11–13] The favorable safety profile and efficacy observed in these phase 3 clinical trials in adults support the continued clinical investigation of imipenem/cilastatin/relebactam in children. When co-administered, both imipenem and relebactam exhibit a dose-proportional pharmacokinetic (PK) profile similar to the PK profile of each individual agent. Imipenem, cilastatin, and relebactam are renally excreted and population PK modeling analysis found that dose adjustment is necessary for children with moderate-to-severe renal impairment.[9,14,15]

The published literature on prospective studies describing the PK and safety of antibacterial agents appropriate for treating multidrug-resistant gram-negative bacterial infections is sparse in neonatal and pediatric populations. Several age-dependent factors, including renal function maturation during infancy and early childhood, can impact PK, resulting in age-dependent differences in antibiotic exposure at sites of infection, which can affect outcomes.[16] Therefore, the objective of this study was to evaluate the PK, safety, and tolerability of a single dose of intravenous imipenem/cilastatin/relebactam and to determine the appropriate dose in neonates, infants, and children based on PK/pharmacodynamic (PD) principles.

Methods

Institutional Review Board (IRB)

All children had a legally acceptable representative or parent(s) who provided documented informed consent for the clinical trial. Assent was obtained from minors in accordance with institutional practices. The study was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate IRBs and regulatory agencies. The names and locations of the study sites and IRB committees are presented in Table S1.

Study Design

This was a phase 1b, open-label, noncomparative, single-dose study (ClinicalTrials.gov identifier, NCT03230916; protocol MK-7655A-020) in children from birth to <18 years of age with confirmed or suspected gram-negative bacterial infection, and was conducted at 21 centers in 8 countries between November 2017 and August 2020. The study was conducted in 2 parts beginning with the parallel enrollment of children from 2 to <18 years of age, followed by the parallel enrollment of children from birth to <2 years of age. In this study, each child was monitored for up to 18 days, which included a screening phase of up to 2 days before receiving a single dose of imipenem/cilastatin/relebactam and then a follow-up period of 14 (+2) days. This study was part of a pediatric investigation plan for imipenem/cilastatin/relebactam.

Children Included in the Study

Eligible children were males and females from birth (≥37 weeks postmenstrual age [gestational age + chronological age at screening]) to <18 years of age receiving standard-of-care antibacterial therapy (following the investigator's discretion) for confirmed or suspected gram-negative bacterial infections. Hospitalized children receiving antibacterial treatment at the time of randomization, or who had recently completed antibacterial treatment for confirmed or suspected gram-negative bacterial infections within 48 hours of study drug administration, and were expected to require ≥24 hours of hospitalization after completion of study drug administration, were eligible for inclusion in this single-dose PK study. Stable renal function, evaluated by estimated creatinine clearance (minimum creatinine clearance ranged from ≥20 mL/min/1.73 m^2 for children from birth to <1 week of age to ≥80 mL/min for children of 12 to <18 years of age), was also one of the eligibility requirements. For the 12 to <18 years age group, creatinine clearance was calculated based on the Cockcroft–Gault equation[17]; for all other age cohorts, creatinine clearance was calculated based on the modified Schwartz equation,[18] with a different *k*-proportionality constant used for neonates.[19]

Exclusion Criteria

Children were excluded from the study if any of the following criteria were met: history of hypersensitivity to imipenem or to any carbapenem, cephalosporin, penicillin, or other β-lactam agent; receipt of carbapenem at any time from ≤48 hours before study drug initiation

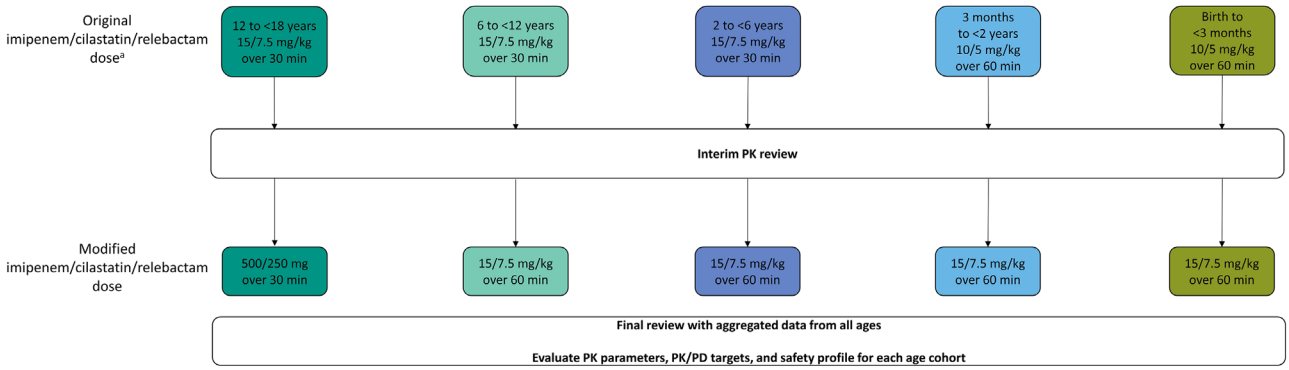

Figure 1. Study design. [a]The original dose for children <2 years of age was determined based on an interim review of PK and safety data from children ≥2 years of age. PD, pharmacodynamic; PK, pharmacokinetic.

through the last PK sample collection; use or planned use of organic anion transporter 1 or organic anion transporter 3 inhibitors, angiotensin receptor blockers, or ketorolac at any time between 1 week before study drug initiation through the last PK sample collection; an expected survival of <72 hours after completion of study drug regime; or history of clinically significant renal, hepatic, or hemodynamic instability.

Treatment and Dose Evaluation

Children were stratified and dosed by age and weight (Figure 1). The original dose of imipenem/cilastatin was 15 mg/kg for children who were 2 to <18 years of age, consistent with the lowest dose recommended on the imipenem/cilastatin label. The original dose of relebactam was 7.5 mg/kg based on the 2:1 ratio of imipenem/cilastatin:relebactam that is recommended for adults. The original dose for imipenem/cilastatin/relebactam in children from birth to <2 years of age was based on the interim review of PK and safety data of the children who were 2 to <18 years of age. Dose modification for each cohort occurred after an interim review of PK and safety data associated with the original dose, based on the first half of the enrolled children, in order to achieve the PD targets with exposures that were considered safe, based on exposure and safety data.

The following parameters were assessed during the interim review to adjust doses in children enrolled subsequently:

- Whether simulated population PK parameters for each age cohort approached the following target values:
  - o ≥30% of the dosing interval with unbound plasma concentrations that exceeded the minimum inhibitory concentration time (%fT>MIC, within a proposed dosing interval) for single-dose imipenem (area under the plasma concentration–time curve from time 0 extrapolated to infinity [$AUC_{0-\infty}$] ≤74.8 mcg·h/mL), established as efficacious and well tolerated in adults[9,15,20,21];
  - o Single-dose relebactam exposure with $AUC_{0-\infty}$ ≥13.1 mcg·h/mL (and ≤69.7 mcg·h/mL), established as well tolerated in adults[9,14,15];
- Acceptable safety profile, including review of any life-threatening toxicities (as defined in the study protocol) considered by the investigator to be related to study treatment.

Assessments

For each child, PK parameters were assessed for 6-12 hours after a single intravenous dose of imipenem/cilastatin/relebactam and safety parameters were assessed for up to 24 hours; a follow-up in-person visit/telephone call to evaluate safety was conducted at 14 (+2) days after infusion. A total of 4 blood samples were obtained from each child for the PK analysis. The PK sample collection methodology (peripherally inserted central catheter line, indwelling catheter access, individual peripheral phlebotomies, arterial line; heel stick for neonates and young infants) was at the discretion of the investigators. All PK samples were drawn within the specified time window and all sampling times were documented (Table 1).

As previously described, plasma concentrations of imipenem, cilastatin, and relebactam were determined using a validated high-performance liquid chromatographic tandem mass spectrometric method (Q^2 Solutions, Ithaca, NY, USA).[14] The analytical range was 0.25 to 100 mcg/mL. The imipenem and relebactam PK data were used to develop a pediatric population PK model, which was used to perform simulations to derive exposure-appropriate pediatric doses. Population PK model-based PK exposures were determined for imipenem and relebactam. Specifically, leveraging a Bayesian framework and using population PK parameters from adults and respective covariate relationships as prior distributions, a PK model comprising both imipenem and relebactam components was

Table 1. Sparse PK Sampling Schedule

	12 to <18 years (n = 7)	6 to <12 years (n = 6)	2 to <6 years (n = 6)	3 months to <2 years (n = 8)	Birth to <3 months (n = 19)
PK sampling schedule					
First sample	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose
Second sample	Within 5 minutes[a]	Within 5 minutes[a]	Within 5 minutes[a]	Within 10 minutes[a]	Within 10 minutes[a]
Third sample	1.5 to 2.5 hours[b]	1.5 to 2.5 hours[b]	1.5 to 2.5 hours[b]	1.5 to 2.5 hours[b]	2 to 5 hours[b]
Fourth sample	4.5 to 6 hours[b]	4.5 to 6 hours[b]	4.5 to 6 hours[b]	4.5 to 6 hours[b]	6 to 12 hours[b]

PK, pharmacokinetic.
[a] After the end of study drug infusion.
[b] After the start of study drug infusion.

developed for a pediatric population.[22,23] For fixed-effect parameters, a multivariate normal prior distribution was used. For both inter-individual variability and residual variability parameters, an inverse Wishart prior distribution was used. The differences in clearance and volumes from the adult population across pediatric cohorts were described via allometric scaling. A standard allometric exponent of 0.75 was added to body weight on clearance and intercompartmental clearance, whereas an allometric exponent of 1 was added to body weight on central volume (V1) and peripheral volume, respectively. This methodology has been comprehensively described previously.[23] Virtual pediatric populations were created using National Health and Nutrition Examination Survey data from 2011 to 2016,[24] and published serum creatinine distributions,[25] comprising age, gender, weight, height, and serum creatinine measurements. These virtual populations (n = 2000 per age cohort) were used to run simulations to evaluate the probability of target attainment for PK/PD targets (imipenem, %fT>MIC ≥30%; relebactam, AUC from 0 to 24 hours ≥38.5 μM·h [13.4 mcg·h/mL]) and safety targets (imipenem, $AUC_{0-\infty}$ ≤216.5 μM·h [64.8 mcg·h/mL], maximum concentration [C_{max}] ≤161 μM [48.2 mcg·h/mL]; relebactam, $AUC_{0-\infty}$ ≤190 μM·h [66.2 mcg·h/mL], C_{max} ≤118 μM [41.1 mcg·h/mL]). Different dosing regimens, with a maximum imipenem dose of 500 mg and a maximum relebactam dose of 250 mg, were evaluated to select a dosing regimen for each age cohort for which the predefined targets were jointly achieved with at least 90% probability of target attainment. Noncompartmental analysis (NCA) was used to summarize the cilastatin PK profile. The PK parameters were calculated using Phoenix WinNonlin 6.3.0.395 (Certara, Princeton, NJ, USA). PK/PD targets were 30% fT>MIC for imipenem and free AUC normalized to MIC (at 2 mcg/mL) of ≥8.0 (equivalent to $AUC_{0-\infty}$ ≥20.52 mcg·h/mL) for relebactam, which is associated with a 2-log kill in preclinical models; the relebactam concentration is fixed because it does not have intrinsic antibacterial activity. This has been previously described.[15,20,23,26–28]

PK End Points

The primary end points were: C_{max} and %fT>MIC for imipenem; C_{max} and AUC from 0 to 6 hours (AUC_{0-6h}) for relebactam; and AUC_{0-6h}, AUC from dosing to the time of the last measured concentration (AUC_{last}), and C_{max} for cilastatin. The primary PK/PD analysis for the primary end points were based on the population of children who had at least 1 post-dose PK data point available.

Safety End Points

The secondary end points included adverse events (AEs) and events of clinical interest.

Statistical Analyses

Data were evaluated with summary statistics; no formal hypothesis testing was planned or performed. The type and incidence of all AEs and serious AEs were tabulated by age and dose level.

The minimum enrollment target was 44 children. The enrollment targets for each age cohort were as follows: 12 to <18 years of age (n ≥ 6); 6 to <12 years of age (n ≥ 6); 2 to <6 years of age (n ≥ 6); 3 months to <2 years of age (n ≥ 8, with ≥4 who were <1 year of age); 4 weeks to <3 months of age (n ≥ 6); 1 to <4 weeks of age (n ≥ 6); and <1 week of age (n ≥ 6). These sample sizes were primarily based on empirical considerations and the feasibility of meeting the study objectives and regulatory requirements. A simulation-based methodology was implemented to determine the appropriate sample size for each pediatric age cohort that would have ≥80% probability to achieve reasonable precision, defined as a 95% confidence interval within 60% to 140% of the population mean (approximately = 20% relative standard error), in the model-based estimation of primary PK parameters for both imipenem and relebactam in each pediatric age cohort.

Pharmacokinetic Methods. The imipenem and relebactam data were used to develop a pediatric population PK model, which was used to perform simulations to derive suitable pediatric doses. For imipenem and relebactam, the analysis was performed using

Table 2. Baseline Characteristics and Demographics, All Randomized Children

Characteristic	12 to <18 years (n = 7)	6 to <12 years (n = 6)	2 to <6 years (n = 6)	3 months to <2 years (n = 8)	Birth to <3 months (n = 20)[a]
Sex, n (%)					
Female	5 (71.4)	5 (83.3)	4 (66.7)	6 (75.0)	8 (40.0)
Weight (kg)					
Mean (SD)	48.8 (4.1)	34.4 (11.7)	15.4 (2.2)	8.6 (1.9)	4.0 (1.1)[b]
Median (range)	48.9 (43-55)	33.5 (19-53)	15.4 (12-19)	8.1 (7-12)	3.8 (3-7)[b]
Estimated CrCl[c]					
Mean (SD)	123.7 (20.5)	167.2 (44.2)	211.1 (85.2)	174.9 (91.7)	79.6 (35.5)[d]
Median (range)	127.8 (83-144)	154.9 (122-246)	218.0 (103-143)	167.7 (53-312)	76.8 (36-149)
Infection type, n					
UTI	3	1	1	5	6
Pneumonia	2	4	2	1	3
Other[e]	2	1	1	1	2
Neutropenic sepsis	0	0	2	0	0
IAI	0	0	0	1	0
Sepsis	0	0	0	0	8

CrCl, creatinine clearance; IAI, intra-abdominal infection; SD, standard deviation; UTI, urinary tract infection.
[a] Only 19 children in this cohort were treated; 1 child did not receive treatment owing to withdrawal of consent by parent/guardian.
[b] n = 19.
[c] For the 12 to <18 years of age group, the units for CrCl are mL/min, as calculated based on the Cockcroft–Gault equation; for all other age cohorts, the units for CrCl are mL/min/1.73 m^2, as calculated based on the modified Schwartz equation.
[d] n = 18.
[e] Infection caused by gram-negative bacteria with no additional infection type information provided on the case report form.

nonlinear mixed-effects modeling (NONMEM 7.2; ICON, Dublin, Ireland). The cilastatin data were used to summarize the PK profile based on NCA. For cilastatin, noncompartmental-based PK parameters were derived using Phoenix WinNonlin 6.3.0.395.

The $AUC_{0-\infty}$, C_{max}, the unbound plasma concentration exceeding the MIC (imipenem only), systemic clearance (CL), and central volume of distribution were the model-based and derived PK parameters calculated for unbound relebactam and/or imipenem. $AUC_{0-\infty}$, C_{max}, concentration at end of infusion (C_{eoi}), half-life, CL, and volume of distribution were the NCA parameters calculated for cilastatin.

Noncompartmental Analysis. Cilastatin concentrations and actual blood sampling times relative to the time of dose were used to determine PK parameters for each child. All values less than the lower limit of quantitation were replaced by zero, both for the calculation of the PK parameters and the summary statistics of the concentrations.

The protocol-scheduled second PK time point was reported as the C_{eoi} sample. Owing to the very limited sparse sampling schedule per child, 1 pre-dose sample and 3 post-dose samples (including C_{max}), the rate constant associated with terminal elimination phase for concentration data (λz) was not calculated. As a result, the PK parameters depending on λz were also not calculated (including $AUC_{0-\infty,}$ CL, and V1). All AUC parameters were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear up/log down). Other NCA PK parameters for cilastatin included C_{eoi} or C_{max}, AUC_{0-6h}, AUC_{last}, the last measured plasma drug concentration (C_{plast}), and time of last measurable concentration (T_{last}).

Results

Enrolled Children

A total of 51 children were screened, 47 were allocated, and 46 received the study medication and completed the study. One child did not receive the study medication because of a withdrawal of consent. Of the 47 allocated children, 46 were included in the safety population and 42 were included in the per-protocol population for the PK analysis. Among children who received the study medication, all completed the study according to the protocol. Demographics and baseline characteristics of children enrolled in the study are summarized by age cohort in Table 2. The majority of the children were female (28/47, 60%). The mean (standard deviation) and median (range) creatinine clearance in the group from birth to <3 months were lower compared with the other age cohorts, as expected for this age group. The most common infection types at baseline were urinary tract infection (16/47, 34%), pneumonia (12/47, 26%), and sepsis (8/47, 17%), confirmed or suspected to be caused by gram-negative bacteria.

PK Parameters

Forty-two children were included in the PK analysis with 4 excluded for protocol deviations, where the

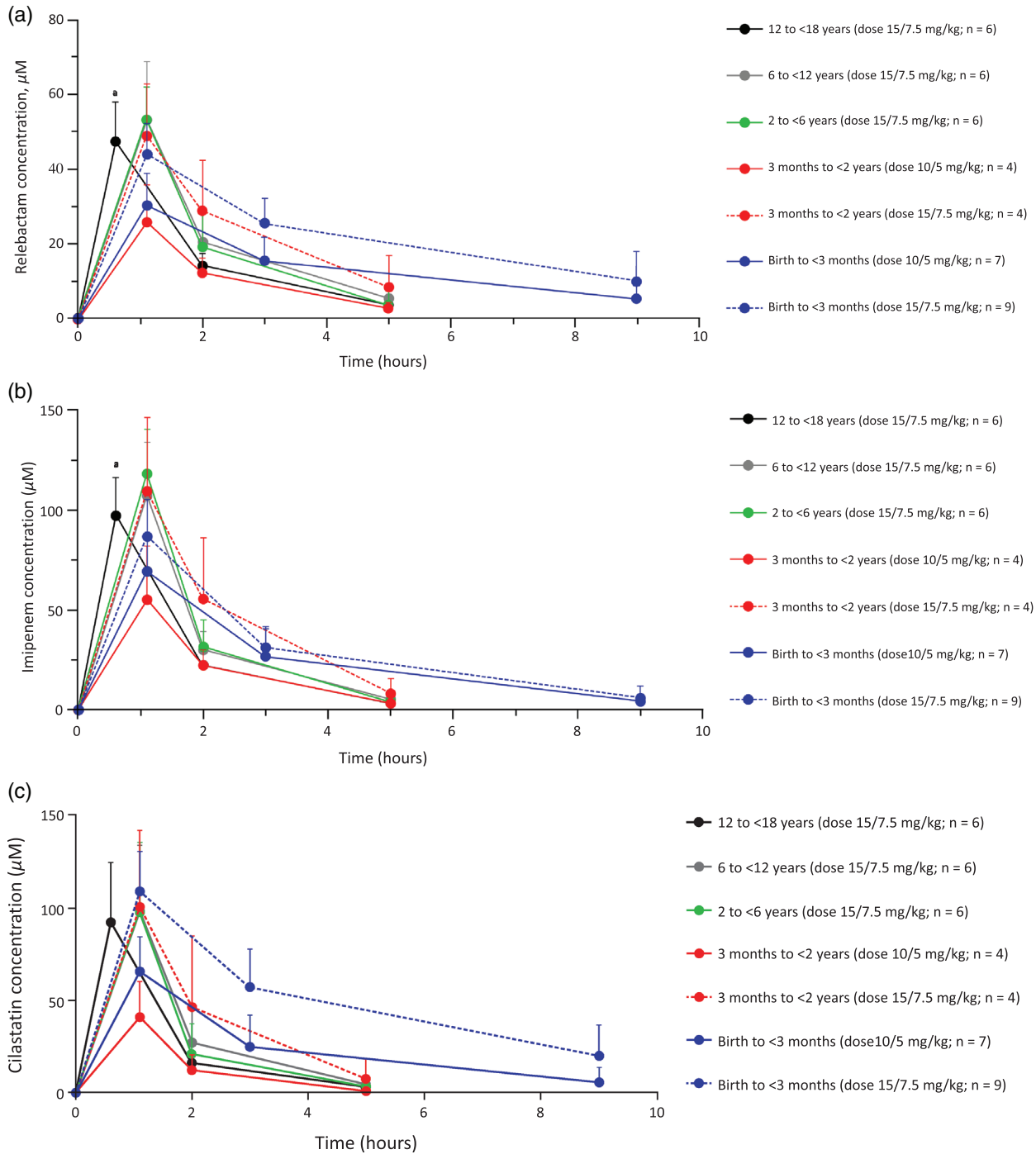

Figure 2. Arithmetic mean (SD) plasma concentration–time profile for imipenem (a), relebactam (b), and cilastatin (c) after the administration of a single IV dose of imipenem/cilastatin/relebactam. Concentrations for this figure are expressed as μM; to convert to mcg·h/mL, multiply by 0.34848 for relebactam and 0.29937 for imipenem. [a]The nominal time after the first dose represents a protocol-defined range of time for each time point; the first post-dose time point was 0.6 hours in the 12 to <18 years of age group, and was 1.1 hours for all other groups. IV, intravenous; SD, standard deviation.

duration of study drug infusion differed from that specified in the protocol. The mean plasma concentration–time profiles for imipenem, cilastatin, and relebactam were generally comparable across age cohorts, as seen in Figure 2. At the modified study doses (determined after interim review, as shown in Figure 1), both imipenem and relebactam exceeded protocol-defined efficacy PK/PD targets in all age cohorts. At the modified doses for all age cohorts, the geometric means for imipenem %fT>MIC and C_{max} ranged from 56.5% to 93.7% and from 32.2 to 38.2 mcg/mL, respectively, and the geometric means for relebactam C_{max}, AUC_{0-6h},

and $AUC_{0-\infty}$ ranged from 16.9 to 21.3 mcg/mL, from 26.1 to 55.3 mcg·h/mL, and from 27.9 to 76.9 mcg·h/mL (Table 3). The exposures for imipenem and relebactam associated with the modified doses exceeded the predefined PK/PD targets for both agents. For cilastatin, at the modified doses for all age cohorts, the geometric means for C_{max} and AUC_{last} ranged from 31.15 to 38.35 mcg/mL and from 32.66 to 122.59 mcg·h/mL (Table 3). Clearance was generally comparable in both imipenem and relebactam across all ages, after accounting for weight.

Safety

A single dose of imipenem/cilastatin/relebactam was generally well tolerated in children from birth to <18 years of age. Overall, 8/46 (17%) children reported at least 1 AE and 2/46 (4%) children reported AEs that were deemed drug related by the investigator (Table 4). No AEs were reported among children from 6 to <12 years of age. There were no serious AEs, discontinuations due to AEs, protocol-defined events of clinical interest, or deaths.

The most commonly reported AEs included anemia (3/46, 7%) and diarrhea (3/46, 7%). Other AEs included decreased neutrophil count (1/46, 2%), increased alanine aminotransferase (1/46, 2%), increased aspartate aminotransferase (1/46, 2%), miliaria (1/46, 2%), nasopharyngitis (1/46, 2%), and thrombocytosis (1/46, 2%). Drug-related AEs, as assessed by investigators, occurred in 2 children, and included increased aspartate aminotransferase (1/46, 2%), increased alanine aminotransferase (1/46, 2%), and anemia (1/46, 2%) in 1 child in the 12 to <18 years of age group, and diarrhea (1/46, 2%) in 1 child in the 2 to <6 years of age group; none were serious and all were mild in severity, with a duration of 5 days.

Discussion

This phase 1b, open-label, noncomparative, single-dose clinical trial was the first to evaluate the PK profile, safety, and tolerability of imipenem/cilastatin/relebactam in children, including neonates. Generally, the concentration–time profiles of imipenem, cilastatin, and relebactam were comparable across all age cohorts, from birth to adolescence. In the youngest age cohorts (birth to <3 months of age, 3 months to <2 years of age), the original dose of 10/5 mg/kg imipenem/cilastatin/relebactam did not produce the relebactam exposures reliably associated with microbiologic and clinical efficacy; therefore, after the interim analysis, the dose was increased to 15/7.5 mg/kg imipenem/cilastatin/relebactam in these cohorts. After this dose increase, the %fT>MIC, AUC_{0-6h}, and AUC_{last} values for imipenem, cilastatin, and relebactam were higher in children from birth to <3 months of age than in other age cohorts. This may be a result of the reduced clearance observed in the youngest cohort, consistent with the existing knowledge of renal function, which tends to be lower during the first months of life, with renal maturation occurring through infancy until 2 years of age. The clearance of renally excreted drugs, including those governed by glomerular filtration and/or tubular secretion, such as imipenem, cilastatin, and relebactam, increase with increasing gestational age, chronological age, and body weight.[9,14–16,29] This study was designed to reduce the potential impact of age-related differences in drug clearance on exposure, with individual dosing by age cohort and weight, and the potential for dose modifications after interim reviews, as well as a 2-part design that used the interim reviews from the 3 oldest age cohorts to inform dose selection for the 2 youngest age cohorts. Overall, for imipenem and relebactam, clearance normalized to body weight was comparable between age cohorts.

Imipenem, cilastatin, and relebactam exhibited dose-proportional PK and imipenem and relebactam exceeded protocol-defined efficacy PK/PD targets across all age cohorts at the full study doses. Although the %fT>MIC values were higher with the 60-minute infusion versus the 30-minute infusion of the 15/7.5 mg/kg dose in the 2 to <6 and 6 to <12 years cohorts, the %fT>MIC values with the 30-minute infusion exceeded the target. Relebactam has no intrinsic antibacterial activity, but rather acts to overcome the loss of carbapenem susceptibility arising from β-lactamase activity and limits the risk of underexposure to imipenem.[30,31] Relebactam inhibits β-lactamase activity and thereby protects hydrolysis of imipenem.[32,33] For relebactam, the PD metric best correlated with outcome in murine PD studies is the ratio between AUC and threshold MIC exposure,[34] which was easily achieved with doses of relebactam used in children in this study.

Notably, the PK/PD targets used in this study are well established, conservative, and consistent with the targets recently used in probability of target attainment analyses performed in adults.[9,15,26,27,34,35]

Overall, a single dose of imipenem/cilastatin/relebactam was well tolerated in these children. In total, 2 children had 4 AEs categorized as drug related by the investigator. Drug-related AEs reported in the study were increased alanine aminotransferase, increased aspartate aminotransferase, anemia, and diarrhea, as assessed by the investigators. Imipenem/cilastatin/relebactam has a well-established safety profile in adults, and these data will enhance the understanding of the safety and tolerability profile of imipenem/cilastatin/relebactam in the pediatric population.[8,10]

Table 3. Imipenem, Relebactam, and Cilastatin Exposures after the Administration of a Single IV Dose of Imipenem/Cilastatin/Relebactam, Presented as Geometric Mean (% Coefficient of Variation)

Age cohort and imipenem/cilastatin/relebactam dose	n	Imipenem				Relebactam					Cilastatin		
		CL (L/h/kg)[a]	CL (L/h)	C_{max} (mcg/mL)	%fT> MIC[b]	CL (L/h/kg)[a]	CL (L/h)	C_{max} (mcg/mL)	AUC_{0-6h} (mcg·h/mL)	$AUC_{0-\infty}$ (mcg·h/mL)	C_{max} (mcg/mL)	AUC_{last} (mcg·h/mL)	$AUC_{0-^{\circ}6h}$ (mcg·h/mL)[c]
12 to <18 years													
500/250 mg over 30 minutes	6	0.26 (17.6)	12.58 (18.4)	32.2 (16.4)	56.5 (17.1)	0.18 (15.5)	8.98 (20.7)	17.2 (23.0)	26.1 (17.1)	27.9 (20.0)	31.15 (41.0)	36.92 (48.0)	—
6 to <12 years													
15/7.5 mg/kg over 30 minutes	1	0.32 (NC)	9.60 (NC)	37.7 (NC)	58.3 (NC)	0.20 (NC)	6.10 (NC)	30.1 (NC)	35.8 (NC)	36.8 (NC)	—	—	—
15/7.5 mg/kg over 60 minutes	2	0.23 (37.2)	5.25 (9.2)	36.8 (20.6)	80.3 (26.7)	0.17 (59.5)	3.96 (28.9)	21.0 (30.7)	39.0 (48.9)	43.1 (59.5)	34.05 (32.0)	44.81 (54.0)	—
500/250 mg over 30 minutes	2	0.25 (7.2)	11.67 (27.6)	34.2 (9.2)	61.6 (25.1)	0.17 (14.8)	8.03 (35.7)	20.0 (26.1)	29.4 (29.4)	31.5 (35.1)	—	—	—
500/250 mg over 60 minutes	1	0.32 (NC)	11.74 (NC)	33.1 (NC)	56.7 (NC)	0.23 (NC)	8.65 (NC)	17.0 (NC)	26.7 (NC)	27.9 (NC)	—	—	—
2 to <6 years													
15/7.5 mg/kg over 30 minutes	3	0.32 (17.9)	5.31 (29.7)	45.0 (6.7)	50.1 (15.7)	0.25 (30.4)	4.20 (40.8)	20.6 (9.1)	29.0 (30.1)	29.9 (32.4)	—	—	—
15/7.5 mg/kg over 60 minutes	3	0.31 (29.2)	4.43 (45.2)	37.5 (25.2)	57.7 (18.8)	0.26 (37.8)	3.65 (54.1)	16.9 (22.9)	27.6 (39.1)	28.5 (42.0)	32.62 (45.0)	32.66 (65.0)	—
3 months to <2 years													
10/5 mg/kg over 60 minutes	4	0.35 (40.4)	3.31 (60.1)	19.4 (29.6)	50.4 (30.5)	0.27 (34.8)	2.56 (54.5)	11.4 (15.0)	17.6 (31.3)	18.4 (33.6)	13.26 (64.0)[d]	10.86 (140.0)	—
15/7.5 mg/kg over 60 minutes	4	0.23 (40.3)	1.70 (48.1)	38.2 (36.0)	73.9 (19.7)	0.17 (53.8)	1.27 (62.9)	20.8 (17.1)	39.7 (39.1)	44.1 (53.7)	33.87 (42.0)	54.49 (63.0)	—
Birth to <3 months													
10/5 mg/kg over 60 minutes	7	0.22 (15.8)	1.10 (26.2)	23.8 (26.4)	70.2 (10.6)	0.16 (17.9)	0.74 (27.0)	11.9 (17.3)	28.4 (16.4)	32.0 (18.3)	22.80 (28.0)	46.96 (44.0)	47.32 (39.0)
15/7.5 mg/kg over 60 minutes	9	0.19 (14.4)	0.66 (20.4)	35.9 (16.8)	93.7 (9.3)	0.10 (32.5)	0.35 (30.7)	21.3 (21.9)	55.3 (15.9)	76.9 (34.1)	38.35 (20.0)	122.59 (42.0)	122.59 (26.0)

%ft>MIC, percentage of time of dosing interval that the unbound plasma concentration exceeded the minimum inhibitory concentration; AUC_{0-6h}, area under the plasma concentration–time curve from 0 to 6 hours; $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from dosing to time of last measured concentration; CL, clearance; C_{max}, maximum concentration; IV, intravenous; MIC, minimum inhibitory concentration; NC, not calculated.

[a] Weight normalized.

[b] Calculation used an MIC value of 2 mcg/mL.

[c] For children of ≥3 months to <18 years of age, AUC_{0-6h} could not be determined because of the limited sampling scheme (no half-life could be calculated) and no sample was taken after 6 hours.

[d] n = 3 because of an outlier.

Table 4. AE Summary During IV Therapy and 14-Day Follow-Up Period, Safety Population

	12 to <18 years	6 to <12 years	2 to <6 years	3 months to <2 years		4 weeks to <3 months		1 to <4 weeks		<1 week		Total
	(n = 7)	(n = 6)	(n = 6)	(n = 4)	(n = 4)	(n = 5)	(n = 2)	(n = 3)	(n = 3)	(n = 2)	(n = 4)	(N = 46)
Imipenem/cilastatin/ relebactam dose (mg/kg)	—	15/7.5	—	10/5	15/7.5	10/5	15/7.5	10/5	15/7.5	10/5	15/7.5	—
Children with, n (%)												
≥1 AE	1 (14.3)	0	3 (50.0)	1 (25.0)	2 (50.0)	1 (20.0)	0	0	0	0	0	8 (17.4)
Drug-related AE[a]	1 (14.3)	0	1 (16.7)	0	0	0	0	0	0	0	0	2 (4.3)
SAE	0	0	0	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0	0	0	0
Discontinued drug because of an AE	0	0	0	0	0	0	0	0	0	0	0	0

The original dose for the 12 to <18 years age group was 15/7.5 mg/kg before interim review; all children received the full adult dose of 500/250 mg imipenem/cilastatin/relebactam based on their weight. Therefore, the dose was modified to 500/250 mg after the interim review. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; SAE, serious adverse event.

[a] Determined by the investigator to be related to the study drug (increased ALT/AST and anemia in 1 child of 14 years of age; and diarrhea in 1 child of 4 years of age).

A strength of this study is that it enrolled very young children (6 children were <1 week of age; 6 children were 1 to <4 weeks of age). Therefore, the data from this study will info appropriate dose selection and the evaluation of imipenem/cilastatin/relebactam safety in neonates/infants through to adolescents. However, the study did not include preterm infants, which limits its applicability to the preterm population; future investigation of imipenem/cilastatin/relebactam in premature infants is warranted. Another limitation was the small sample size, resulting in as few as 6 children being enrolled in several age cohorts included in the PK population. However, it is well recognized that enrollment in pediatric PK studies has unique scientific, regulatory, and ethical challenges.[36] The use of PK NCA methods as presented in this study has limitations, as sparse PK sampling was conducted in all cohorts. Nonetheless, the data collected in this study provide information that can be used in future population PK analyses.

Conclusions

This single-dose study demonstrated that imipenem, cilastatin, and relebactam each have a generally similar drug exposure profile at the modified doses studied across age cohorts. Imipenem and relebactam exceeded protocol-defined PK/PD targets at the age- and weight-adjusted modified doses administered. Imipenem/cilastatin/relebactam may be an important treatment option for children with serious infections caused by imipenem/cilastatin/relebactam-susceptible strains of gram-negative bacteria resistant to other antibacterial drugs, and these results support further clinical evaluation in targeted pediatric populations with complicated urinary tract infections, complicated intra-abdominal infections, and hospital-acquired/ventilator-associated bacterial pneumonia. These model-informed results have already enabled imipenem/cilastatin/relebactam dose selection for ongoing pediatric clinical evaluation of safety and efficacy in these infections (ClinicalTrials.gov identifier, NCT03969901).

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Author Contributions

All authors are responsible for the work described in this article and meet International Committee of Medical Journal Editors (ICMJE) authorship criteria. All authors were involved in at least one of the following: conception, design of work or acquisition, analysis, and interpretation of data; and drafting the article and/or revising/reviewing the article for important intellectual content. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

M.P., A.M., Y.Z., and A.P. are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. Rahway, NJ, USA (MSD), who may own stock and/or hold stock options in the company. L.F.C. and P.V. were employees of MSD at the time of study conduct. J.S.B. and C.T. report funding to conduct the study from MSD to their institutions. E.R. and M.S.K. report grant funding and consulting fees from MSD to their institutions. N.M. has no potential conflicts of interest to disclose.

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Data Availability Statement

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to Data Access mailbox.

References

1. Meropol SB, Haupt AA, Debanne SM. Incidence and outcomes of infections caused by multidrug-resistant *Enterobacteriaceae* in children, 2007–2015. *J Pediatric Infect Dis Soc*. 2018;7(1):36-45.
2. Chiotos K, Tamma PD, Flett KB, et al. Increased 30-day mortality associated with carbapenem-resistant Enterobacteriaceae in children. *Open Forum Infect Dis*. 2018;5(10):ofy222.
3. Maltezou HC, Kontopidou F, Katerelos P, Daikos G, Roilides E, Theodoridou M. Infections caused by carbapenem-resistant Gram-negative pathogens in hospitalized children. *Pediatr Infect Dis J*. 2013;32(4):e151-e154.
4. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. Accessed April 18, 2022. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed
5. Karlowsky JA, Lob SH, Raddatz J, et al. In vitro activity of imipenem/relebactam and ceftolozane/tazobactam against clinical isolates of Gram-negative bacilli with difficult-to-treat resistance and multidrug-resistant phenotypes—study for monitoring antimicrobial resistance trends, United States 2015–2017. *Clin Infect Dis*. 2021;72(12):2112-2120.
6. Theuretzbacher U. Global antimicrobial resistance in Gram-negative pathogens and clinical need. *Curr Opin Microbiol*. 2017;39:106-112.
7. Center for Disease Control and Prevention. Antibiotic resistance threats in the United States 2019. Accessed August 18, 2023. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.
8. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis*. 2020;70(9):1799-1808.
9. RECARBRIO™ (Imipenem/Cilastatin and Relebactam). US prescribing information. Merck Sharp & Dohme LLC; 2022.
10. Titov I, Wunderink RG, Roquilly A, et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 study). *Clin Infect Dis*. 2020;ciaa803.
11. Karlowsky JA, Lob SH, Kazmierczak KM, et al. *In vitro* activity of imipenem/relebactam against Gram-negative ESKAPE pathogens isolated in 17 European countries: 2015 SMART surveillance programme. *J Antimicrob Chemother*. 2018;73(7):1872-1879.
12. 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;10(3):274-281.
13. Karlowsky JA, Lob SH, Young K, Motyl MR, Sahm DF. Activity of imipenem-relebactam against multidrug-resistant *Pseudomonas aeruginosa* from the United States – SMART 2015–2017. *Diagn Microbiol Infect Dis*. 2019;95(2):212-215.
14. Rhee EG, Rizk ML, Calder N, et al. Pharmacokinetics, safety, and tolerability of single and multiple doses of relebactam, a β-lactamase inhibitor, in combination with imipenem and cilastatin in healthy participants. *Antimicrob Agents Chemother*. 2018;62(9):e00280-18.
15. Patel M, Bellanti F, Daryani NM, et al. Population pharmacokinetic/pharmacodynamic assessment of imipenem/cilastatin/relebactam in patients with hospital-acquired/ventilator-associated bacterial pneumonia. *Clin Transl Sci*. 2022;15(2):396-408.
16. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmaceutics*. 2011;3(1):53-72.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
18. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629-637.
19. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. *J Pediatr*. 1984;104(6):849-854.

20. Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis*. 2007;44(1):79-86.
21. Lala M, Brown M, Kantesaria B, Walker B, Paschke A, Rizk ML. Simplification of imipenem dosing by removal of weight-based adjustments. *J Clin Pharmacol*. 2019;59(5):646-653.
22. Bhagunde P, Patel P, Lala M, et al. Population pharmacokinetic analysis for imipenem–relebactam in healthy volunteers and patients with bacterial infections. *CPT: Pharmacometrics Syst Pharmacol*. 2019;8(10):748-758.
23. Vaddady P, Bhagunde P, Xu M, et al. Application of Bayesian methodology to inform imipenem/relebactam pediatric study design. *Presented at: Population Approach Group Europe (PAGE)*; June 11–14, 2019; Stockholm, Sweden.
24. Center for Disease Control and Prevention. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Accessed August 18, 2023. https://wwwn.cdc.gov/nchs/nhanes/Default.aspx
25. Savory D. Reference ranges for serum creatinine in infants, children and adolescents. *Ann Clin Biochem*. 1990;27(2):99-101.
26. Daryani N, Patel M, Flattery A, Young K, Rizk ML. Imipenem/relebactam pharmacokinetic/pharmacodynamic analyses from an in vivo neutropenic mouse delayed lung infection model [abstract 2086]. Presented at: European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 18–21, 2020; Paris, France.
27. Patel M, Daryani NM, Feng H-P, et al. Imipenem/relebactam pharmacokinetic/pharmacodynamic analyses from an in vivo neutropenic murine thigh infection model [abstract 1693]. Presented at: European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 18–21, 2020; Paris, France.
28. O'Donnell JN, Lodise TP. New perspectives on antimicrobial agents: imipenem-relebactam. *Antimicrob Agents Chemother*. 2022;66(7):e0025622.
29. van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental changes in pharmacokinetics and pharmacodynamics. *J Clin Pharmacol*. 2018;58(suppl 10):S10-S25.
30. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against Enterobacteriaceae and Pseudomonas aeruginosa. *J Antimicrob Chemother*. 2013;68(10):2286-2290.
31. Young K, Painter RE, Raghoobar SL, et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against *Pseudomonas aeruginosa*. *BMC Microbiol*. 2019;19(1):150.
32. Horner C, Mushtaq S, Livermore DM. Potentiation of imipenem by relebactam for Pseudomonas aeruginosa from bacteraemia and respiratory infections. *J Antimicrob Chemother*. 2019;74(7):1940-1944.
33. Wu J, Racine F, Wismer MK, et al. Exploring the pharmacokinetic/pharmacodynamic relationship of relebactam (MK-7655) in combination with imipenem in a hollow-fiber infection model. *Antimicrob Agents Chemother*. 2018;62:e0232317.
34. Mavridou E, Melchers RJ, van Mil AC, Mangin E, Motyl MR, Mouton JW. Pharmacodynamics of imipenem in combination with β-lactamase inhibitor MK7655 in a murine thigh model. *Antimicrob Agents Chemother*. 2015;59(2):790-795.
35. Bhagunde P, Zhang Z, Racine F, et al. A translational pharmacokinetic/pharmacodynamic model to characterize bacterial kill in the presence of imipenem-relebactam. *Int J Infect Dis*. 2019;89:55-61.
36. Coppini R, Simons SHP, Mugelli A, Allegaert K. Clinical research in neonates and infants: challenges and perspectives. *Pharmacol Res*. 2016;108:80-87.

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