1159. Pharmacokinetics, Safety, and Tolerability of Imipenem/Cilastatin/Relebactam in Pediatric Participants With Confirmed or Suspected Gram-negative Bacterial Infections: A Phase 1b, Open-label, Single-Dose Clinical Trial

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Session: P-64. Pediatric Bacterial Studies (natural history and therapeutic)

Background. Imipenem/cilastatin/relebactam (IMI/REL) is approved for treating hospital-acquired/ventilator-associated bacterial pneumonia, complicated urinary tract infection, and complicated intra-abdominal infection in adults. This study assessed single-dose pharmacokinetics (PK), safety, and tolerability of IMI/REL in neonatal and pediatric participants with confirmed or suspected gram-negative bacterial infections.

Methods. This was a phase 1, open-label, non-comparative study (NCT03230916). Age- and weight-adjusted dosing is summarized in Table 1. The primary objective was to characterize the PK profiles for imipenem and relebactam after a single intravenous dose of IMI/REL. PK parameters were analyzed using population modeling. The PK target for imipenem was the percent time of the dosing interval that the unbound plasma concentration exceeded the minimum inhibitory concentration (%fT >MIC) of ≥30% (MIC used, 2 µg/mL). The PK target for relebactam was an area under the curve (AUC)/MIC ratio >8 (MIC used, 2 µg/mL), corresponding to AUC0-24h >58.88 µM·h. Safety and tolerability were assessed for up to 14 days after drug infusion.

Table 1. Summary of Dosing and PK Sampling Schedule by Age Cohort

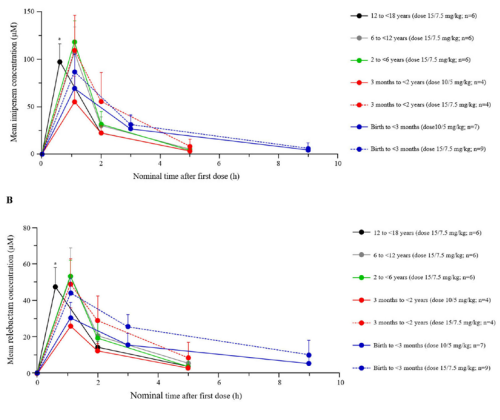
	12 to <18 years (n=7)	6 to <12 years (n=6)	2 to <6 years (n=6)	3 months to <2 years (n=8)	Birth to <3 months (n=19)
Dosing regimen[a]	15/7.5 mg/kg over 30 min or 500/250 mg over 30 min	15/7.5 mg/kg over 30 min or 15/7.5 mg/kg over 60 min	15/7.5 mg/kg over 30 min or 15/7.5 mg/kg over 60 min	10/5 mg/kg over 60 min or 15/7.5 mg/kg over 60 min	10/5 mg/kg over 60 min or 15/7.5 mg/kg over 60 min
PK sampling schedule					
First sample	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose
Second sample	Within 5 min[b]	Within 5 min[b]	Within 5 min[b]	Within 10 min[b]	Within 10 min[b]
Third sample	1.5-2.5 hours[c]	1.5-2.5 hours[c]	1.5-2.5 hours[c]	1.5-2.5 hours[c]	2-5 hours[c]
Fourth sample	4.5-6 hours[c]	4.5-6 hours[c]	4.5-6 hours[c]	4.5-6 hours[c]	6-12 hours[c]

PK, pharmacokinetic.
[a]Protocol-defined interim review resulted in dose and/or infusion time modifications. Initial dose is listed first, followed by modified dose. An approximate 1:1 ratio of participants receiving the initial dose to participants receiving the modified dose was achieved in this study.
[b]After the end of study drug infusion.
[c]After the start of study drug infusion.

Results. Of the 46 participants who received IMI/REL, 42 were included in the PK analysis. The mean plasma concentration-time profiles for imipenem and relebactam were generally comparable across age cohorts (Figure). For imipenem, the geometric mean %fT >MIC ranged from 50% to 94% and the mean maximum concentration (C_{max}) ranged from 65 µM to 126 µM (Table 2). For relebactam, the geometric C_{max} ranged from 33 µM to 87 µM and mean $AUC_{0\text{-}6h}$ ranged from 51 µM·h to 159 µM·h across the age cohorts (Table 2). IMI/REL was well tolerated with 8 (17.4%) participants experiencing ≥1 adverse events (AE) and 2 (4.3%) participants experiencing AE that were deemed drug related by the investigator. Drug-related AE were increased alanine aminotransferase, increased aspartate aminotransferase, anemia, and diarrhea, which were non-serious, mild in severity, and resolved within the follow-up period of 14 days.

Figure 1

Figure. Arithmetic Mean (±SD) Plasma Concentration-Time Profile for Imipenem (A) and Relebactam (B), After the Administration of a Single Intravenous Dose of IMI/REL



IMI/REL, imipenem/cilastatin/relebactam. [a]The nominal time after 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 group and 1.1 hours for all other groups.

Table 2. Imipenem and Relebactam Exposures After the Administration of a Single Intravenous Dose of IMI/REL, Presented as Geometric Mean (% Coefficient of Variation)

		Imipenem		Relebactam	
Age cohort and IMI/REL dose	n	C_{max} (µM)[a]	%fT>MIC[b] (µM·h)	C_{max} (µM)[a]	$AUC_{0\text{-}6h}$ (µM·h)
12 to <18 years					
500/250 mg over 30 min	6	107.6 (16.4)	56.5 (17.1)	49.3 (23.0)	74.8 (17.1)
6 to <12 years					
15/7.5 mg/kg over 30 min	1	126.0 (NC)	58.3 (NC)	86.5 (NC)	102.6 (NC)
15/7.5 mg/kg over 60 min	2	123.0 (20.6)	80.3 (26.7)	60.3 (30.7)	111.8 (48.9)
500/250 mg over 30 min	2	114.2 (9.2)	61.6 (25.1)	57.4 (26.1)	84.5 (29.4)
500/250 mg over 60 min	1	110.6 (NC)	56.7 (NC)	48.7 (NC)	76.6 (NC)
2 to <6 years					
15/7.5 mg/kg over 30 min	3	150.3 (6.7)	50.1 (15.7)	59.1 (9.1)	83.1 (30.1)
15/7.5 mg/kg over 60 min	3	125.1 (25.2)	57.7 (18.8)	48.6 (22.9)	79.2 (39.1)
3 months to <2 years					
10/5 mg/kg over 60 min	4	64.9 (29.6)	50.4 (30.5)	32.7 (15.0)	50. 6 (31.3)
15/7.5 mg/kg over 60 min	4	127.7 (36.0)	73.9 (19.7)	59.6 (17.1)	114.0 (39.1)
Birth to <3 months					
10/5 mg/kg over 60 min	7	79.4 (26.4)	70.2 (10.6)	34.2 (17.3)	81.6 (16.4)
15/7.5 mg/kg over 60 min	9	119.8 (16.8)	93.7 (9.3)	61.0 (21.9)	158.8 (15.9)

$AUC_{0\text{-}6h}$, area under the curve from 0 to 6 hours; C_{max}, maximum concentration; IMI/REL, imipenem/cilastatin/relebactam; MIC, minimum inhibitory concentration; NC, not calculated.
[a]To convert to µg/mL, multiply by 0.34848 for relebactam and 0.29937 for imipenem.
[b]Calculation used a threshold MIC value of 2 µg/mL.

Conclusion. Imipenem and relebactam exceeded the pediatric plasma PK targets across pediatric age cohorts in the study; the single doses of IMI/REL were well tolerated. These results will inform IMI/REL dose selection for further pediatric clinical evaluation.

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1160. Predictive Factors to Guide Empiric Antimicrobial Therapy of Acute Hematogenous Osteomyelitis in Children

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Background. Acute hematogenous osteomyelitis (AHO) is a serious infection in children. ESPID guidelines recommend empiric therapy with antistaphylococcal β-lactams in regions with a low methicillin-resistant *S. aureus* (MRSA) prevalence. In areas with a moderate-high prevalence of MRSA, selection of empiric therapy can be more challenging. We sought to examine factors present at the time of admission which may predict etiology and guide treatment in pediatric AHO in a region with endemic MRSA.

Methods. We reviewed admissions with ICD9/10 codes for AHO from 2011-2020 in otherwise healthy children. Patients with chronic infection, open or penetrating trauma, orthopedic hardware *in situ*, or disease secondary to a contiguous focus were excluded. Medical records were reviewed for clinical and laboratory parameters present on the day of admission.

Results. 586 cases were included. An etiology was identified in 76.8% of cases and *S. aureus* was most commonly identified (66.2%, 19% MRSA, Figure 1). Infection due to *Kingella kingae* (0.7%) occurred in younger children (p=0.01). Significant differences in presenting features were noted across pathogens, although *S. aureus* dominated in all sub-groups (Figure 2). Among children with respiratory symptoms at presentation, Group A *Streptococcus* (GAS, 10.7%), and *S. pneumoniae* (2.6%, p=0.01) were identified twice as frequently. Among children with reptiles exposure, *Salmonella* was identified in 10.8% (p=0.04). Multifocal infections and those requiring ICU admission were due to *S. aureus* in 88% and 97% of cases, respectively; these cases were disproportionately MRSA (36.4%, p=0.01 and 54%, p< 0.001). Both ESR and CRP were higher among MRSA compared to any other pathogen (Figure 3, p< 0.01). A CRP at presentation > 7 mg/dl had a 79.6% sensitivity for MRSA infection with a negative predictive value of 91.5%. Among those with either an ESR > 50 mm/hr or a CRP > 7 mg/dl, an organism was identified in 83.2%

Figure 1. Etiology of AHO, 2011-2020