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Open-Label Study To Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Doripenem in Infants Less than 12 Weeks in Chronological Age

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Doripenem, a parenteral carbapenem with broad-spectrum activity against aerobic Gram-negative and Gram-positive and anaerobic pathogens, is currently approved for use in adults in the United States and European Union. Single-dose doripenem pharmacokinetics in 52 infants <12 weeks in chronological age were investigated in this phase 1 study. Hospitalized, medically stable infants <12 weeks in chronological age were stratified into 6 groups based on chronological and gestational age designed to reflect increasing renal maturation and decreasing volume of distribution (V_z) for β-lactam antimicrobials during the first 3 months of life. Subjects received single-dose doripenem (5 mg/kg of body weight for <8 weeks and 8 mg/kg for ≥8 weeks in chronological age) administered intravenously over 1 h. Plasma samples were obtained immediately before the end of the infusion and 1.5, 3, and 7 h after the start of the infusion. Urine was obtained by indwelling catheter during the 8 h following infusion. Doripenem showed linear pharmacokinetics across the 6 age groups. Neonates (<4 weeks in chronological age) had increased mean exposure (area under the plasma concentration-time curve from time zero to infinite time [AUC_∞], 45.7 versus 32.4 μg · h/ml), longer elimination half-life (2.98 versus 1.79 h), and lower clearance (2.03 versus 3.03 ml/min/kg) compared with infants >4 weeks. Mean V_z was highest in subjects with the earliest gestational age (<32 weeks): 0.564 liter/kg for neonates and 0.548 liter/kg for infants. Single-dose pharmacokinetics of doripenem administered as a 1-hour infusion in term and preterm infants <12 weeks in chronological age were similar to what has been observed in neonates and very young infants with other carbapenems. Single-dose doripenem was generally safe and well tolerated. (This study has been registered with ClinicalTrials.gov under registration no. NCT01381848 and with EudraCT under registration no. 2009-014387-20.)

Carbapenems have been used safely in newborns, children, and adolescents for empirical and directed treatment of a variety of infections (1–5).

Only imipenem has the same indications in adults and in neonates (6). No other carbapenems have been approved by the U.S. Food and Drug Administration or European Medicines Agency for neonates or young infants ≤3 months of age, although investigations with meropenem have been conducted in neonates and are ongoing (6–9). Meropenem is approved for bacterial meningitis or complicated intra-abdominal infections in adults and infants aged >3 months, and ertapenem is approved for complicated intra-abdominal, urinary tract, and (sub)cutaneous infections, and community-acquired pneumonia in adults and children (>3 months) (6). Doripenem has not been approved for any indications in children in the United States or European Union (6) but is approved for use in pediatric patients in Japan (10).

Doripenem for injection is a sterile, synthetic, parenteral antibiotic of the carbapenem class of β-lactam antibiotics with broad-spectrum, potent, antibacterial activity against aerobic and anaerobic Gram-negative and Gram-positive pathogens, including extended-spectrum β-lactamase-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa* (11–19). It exerts its activity by targeting penicillin-binding proteins to inhibit the biosynthesis of the bacterial cell wall.

Single- and multiple-dose pharmacokinetics of doripenem have been investigated in several studies in Western and Japanese adult populations. Doripenem exhibited predictable, linear, and time-independent pharmacokinetics across all studies. Renal excretion is the major route of elimination of doripenem, which is excreted mainly unchanged in urine, with approximately 70% of the administered dose recovered in urine as doripenem, and approximately 15% recovered in urine as doripenem-M-1, the major metabolite of doripenem, which is not microbiologically active (20, 21).

The safety and efficacy of doripenem have been evaluated in phase 1, 2, and 3 studies in adult subjects with complicated urinary tract infection, complicated intra-abdominal infection, and nosocomial pneumonia, including ventilator-associated pneumonia. No important differences in safety were seen that warrant special precautions for the use of doripenem based on age, sex, race, or mild renal impairment.

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Compared with adults, infants and children have physiologic differences that affect drug disposition (22, 23). For drugs such as doripenem that have renal elimination, developmental changes after birth alter renal clearance from the plasma compartment directly (23). In addition, the body composition of neonates and young infants is different from that of adults, with relatively larger fluid compartments where a drug may be distributed (22). Consequently, volumes of distribution adjusted for body weight (V_z/BW) tend to be larger in children, particularly neonates (22).

Carbapenems, with the exception of ertapenem, are almost completely unbound to proteins in plasma and are water soluble with an extracellular distribution. The larger extracellular fluid volume, which results in a higher volume of distribution, along with maturational changes in renal elimination is likely to affect pharmacokinetics of carbapenems in neonates (6).

Pharmacokinetics, safety, and tolerability of single doses of doripenem have been studied in children (≥3 months to <18 years of age) who were hospitalized and received antibiotic treatment for bacterial infection or prophylaxis. It was demonstrated that the pharmacokinetics and systemic exposure of doripenem and its major metabolite (doripenem-M-1) in children 3 months to <2 years of age (10 mg/kg of body weight) and in children 2 years to <18 years of age (15 mg/kg; maximum, 500 mg) were within the range previously observed in healthy adult subjects after the administration of doripenem at a single dose of 500 mg administered over 1 h (I. Cirillo, N. Vaccaro, J. Massarella, B. Casteñeda-Ruiz, R. Redman, and J. Bradley, poster presented at the 44th American Society of Health-System Pharmacists [ASHP] Midyear Clinical Meeting and Exhibition, Las Vegas, NV, 6 to 10 December 2009). There was a trend toward a decrease in weight-corrected systemic clearance with increasing age (15 to <18 years of age) with values approaching those observed in healthy adult subjects (Cirillo et al., poster). Doripenem half-life (approximately 1 h) values were similar across all older age groups and are consistent with historical data in healthy adult subjects (Cirillo et al., poster). Doripenem-M-1 exposure parameters followed the same trends as doripenem (Cirillo et al., poster).

The primary objectives of this study were to evaluate pharmacokinetics, safety, and tolerability of doripenem after single-dose administration to neonates (term and preterm) and young infants <12 weeks in chronological age (CA). Data from this trial were intended to help guide doripenem dosing regimens for use in treatment studies in this age group.

MATERIALS AND METHODS

Study design. This was a multicenter, open-label, single-dose, phase 1 pharmacokinetic study (ClinicalTrials.gov registration no. NCT01381848 /EudraCT registration no. 2009-014387-20) in hospitalized but medically stable neonates (term and preterm) and infants <12 weeks in CA. Eligible subjects had documented, or were at risk for, bacterial infection and were receiving treatment with intravenous (i.v.) antibiotics. Doripenem was administered alone at any time after the first dose of a nonstudy antibiotic administered as treatment or prophylaxis. In this study, doripenem was not used to treat infection and did not replace the subject's prescribed antibiotic(s). Subjects were excluded if they had clinically significant abnormal values for hematology or clinical chemistry, or abnormal physical examination or vital signs, including hemodynamic instability; compromised renal function, including renal failure; history of clinically significant allergies to medications, especially known hypersensitivity or intolerance to β-lactam antibiotics; or concomitant use of probenecid, valproic acid, or imipenem-cilastatin, which have documented interactions with doripenem. The study protocol and its amendments were reviewed by each participating institution's independent ethics committee and/or an institutional review board. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with Good Clinical Practices and all applicable regulatory requirements. Known instances of nonconformance were documented and were not considered to have an effect on the overall conclusions of the study. A parent or a subject's legally acceptable representative provided written informed consent.

Subjects were categorized as either neonates (<4 weeks in CA) or infants (≥4 to <12 weeks in CA) and were stratified into 6 age groups based on gestational age (GA) (<32 or ≥32 weeks) and CA: group 1 (neonates <32 weeks in GA and <14 days in CA), group 2 (neonates <32 weeks in GA and ≥14 days to <4 weeks in CA), group 3 (neonates ≥32 to ≤44 weeks in GA and <14 days in CA), group 4 (neonates ≥32 to ≤44 weeks in GA and ≥14 days to <4 weeks in CA), group 5 (infants <32 weeks in GA and 4 to <12 weeks in CA), and group 6 (infants ≥32 to ≤44 weeks in GA and 4 to <12 weeks in CA). Each subject participated in a pretreatment screening phase of ≤2 days (days −2 to −1), a 1-day open-label treatment phase (day 1), a posttreatment phase within 24 h postinfusion or at the time of early withdrawal (day 1), and a follow-up safety assessment (day 7). Subjects remained in the hospital for the duration of the open-label treatment phase to end-of-study procedures (day 1).

Study drug administration. Doses of 5 mg/kg and 8 mg/kg were chosen for evaluation in this study by modeling and simulation of the pharmacokinetic data in pediatric subjects 3 months to <18 years in CA from the completed doripenem single-dose pharmacokinetics and safety study (Cirillo et al., poster). These doses were predicted and intended to achieve exposures similar to those observed in adults receiving a doripenem 500-mg 1-hour infusion and generally associated with clinical and microbiologic efficacy in adults. All subjects received doripenem as a 5-mg/ml i.v. infusion solution. Subjects <8 weeks in CA received doripenem at 5 mg/kg, and subjects ≥8 weeks in CA received doripenem at 8 mg/kg. Doripenem was administered as a continuous 1-hour infusion via a central or peripheral venous line, in a separate line from the infusion of other nonstudy antibiotics or parenteral nutrition.

Pharmacokinetic assessments. Four 0.2-ml blood samples were collected from all subjects for measurement of doripenem at the end of the 1-hour infusion and at 1.5, 3, and 7 h after the start of the infusion. The sample times were based on the concentration-time profile of doripenem in adults and older children. Urine was collected from catheterized subjects only over the interval of 0 (start of doripenem infusion) to 8 h after the start of the infusion. From each interval collection (0 to 8 h), a 1-ml aliquot was used for the measurement of doripenem concentration in urine. Blood samples were collected in glass tubes and centrifuged at 4°C for 10 min to yield plasma, which was transferred to a labeled polypropylene vial and immediately stored at −70°C until analysis. For urine collections, total volumes were measured, and after gentle mixing, 3-ml aliquots were transferred to labeled vials and stored frozen at −70°C until analysis. Plasma and urine were analyzed for determination of doripenem using a previously validated, specific, and sensitive liquid chromatography method coupled to tandem mass spectrometry. The method had a linear range of 0.1 to 50 μg/ml for doripenem, with the lower limit of quantitation equal to 0.1 μg/ml. The doripenem method precision (percent coefficient of variation) of calibration standards ranged from 1.1% to 8.6%. The accuracy of the back-calculated values of the calibration standards as measured by the percent from nominal value ranged from 96.6% to 107.0%. The mean coefficients of determination (r^2) for all analytical batches met acceptance criteria of ≥0.98.

For all subjects, the following plasma pharmacokinetic parameters were determined via noncompartmental analysis with validated WinNonlin v.5.2 (Pharsight Corporation, Mountain View, CA, USA) software: maximum observed plasma concentration (C_{max}), observed plasma concentration at the end of the doripenem infusion (C_{inf}), time to reach C_{max} (t_{max}), time associated with C_{inf}, area under the concentration-time

TABLE 1 Demographic and baseline characteristics

Characteristic	Neonate (<4 wk in CA)				Infant (4 to <12 wk in CA)		Total
	<32 wk in GA		≥32 to ≤44 wk in GA				
	<14 days in CA; group 1	≥14 days in CA; group 2	<14 days in CA; group 3	≥14 days in CA; group 4	<32 wk in GA; group 5	≥32 to ≤44 wk in GA; group 6	
n	8	9	9	8	7	11	52
Age (days)[a]							
Mean (SD)	3.6 (3.34)	19.0 (3.61)	3.7 (2.35)	16.6 (2.88)	52.0 (12.99)	43.2 (13.60)	23.2 (19.97)
Median (range)	2.0 (1–11)	19.0 (14–23)	3.0 (1–9)	16.5 (14–23)	54.0 (31–74)	40.0 (29–65)	17.0 (1–74)
GA (wk)							
Mean (SD)	28.9 (1.96)	27.1 (1.54)	35.4 (3.00)	37.8 (1.67)	28.0 (2.00)	38.0 (2.37)	32.9 (5.14)
Median (range)	29.0 (25–31)	27.0 (25–29)	34.0 (32–40)	38.0 (34–39)	27.0 (25–30)	38.0 (34–41)	33.0 (25–41)
Sex, *n* (%)							
Female	4 (50)	3 (33)	5 (56)	5 (63)	5 (71)	6 (55)	28 (54)
Male	4 (50)	6 (67)	4 (44)	3 (38)	2 (29)	5 (45)	24 (46)
Race, *n* (%)							
White	8 (100)	8 (89)	7 (78)	7 (88)	7 (100)	6 (55)	43 (83)
Multiple	0	0	0	0	0	1 (9)	1 (2)
Black or African American	0	1 (11)	1 (11)	1 (13)	0	0	3 (6)
Asian	0	0	0	0	0	1 (9)	1 (2)
Other	0	0	1 (11)	0	0	1 (9)	2 (4)
Unknown	0	0	0	0	0	2 (18)	2 (4)
Ethnicity, *n* (%)							
Hispanic or Latino	0	0	0	1 (13)	0	1 (9)	2 (4)
Not Hispanic or Latino	8 (100)	9 (100)	9 (100)	7 (88)	7 (100)	9 (82)	49 (94)
Not reported	0	0	0	0	0	1 (9)	1 (2)
Baseline wt (kg)							
Mean (SD)	1.31 (0.352)	1.20 (0.312)	2.57 (0.683)	3.37 (0.401)	2.07 (0.597)	4.16 (0.893)	2.53 (1.259)
Median (range)	1.28 (0.9–2.0)	1.21 (0.7–1.6)	2.44 (1.6–3.9)	3.29 (2.7–4.0)	1.98 (1.4–2.9)	4.47 (2.7–5.4)	2.47 (0.7–5.4)

[a] Age (days) is the CA at time of doripenem infusion collected on the case report form.

curve (AUC) from time zero to time of last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time zero to infinite time (AUC_{∞}), elimination half-life ($t_{1/2}$), total clearance of drug after i.v. administration (CL), apparent volume of distribution for the terminal phase (V_z), metabolite-to-parent ratio for C_{max} (M/P C_{max} ratio), and M/P AUC_{last} ratio. The following urine pharmacokinetic parameters were determined for doripenem based on the individual urine concentration-time data: amount excreted into the urine for the 0- to 8-hour interval (Ae), amount excreted into the urine expressed as a percentage of the administered dose (Ae, %dose), and renal clearance. Creatinine clearance (CL_{CR}) was estimated using the Schwartz equation (24–26). CL_{CR} was calculated as [$k \times$ length (centimeters)]/Cr (milligrams/deciliter), where k is a rate constant equal to 0.45, length (centimeters) is the length at the 50th percentile for a subject (fetal infant growth chart for preterm infants used for subjects <37 weeks in GA [27]; World Health Organization growth charts, as recommended by the Centers for Disease Control and Prevention for infants from birth to 24 months, used for ≥37 weeks in GA [28, 29]), and Cr is the serum creatinine concentration in milligrams per deciliter.

In an exploratory analysis, the time and percent time above a doripenem concentration of 1 μg/ml ($T>$MIC and $\%T>$MIC, respectively), assuming that the great majority of neonatal pathogens have a MIC of ≤1 μg/ml, were determined based on individual subject simulated plasma concentration data and sampling times from 0 to 8 h via noncompartmental analysis with validated WinNonlin v5.2.1 software.

Safety assessments. Safety from screening to the follow-up visit was evaluated by examining incidence, severity, relation to study drug, and type of adverse events; changes in clinical laboratory results, physical examination, and vital sign measurements; and concomitant medication/therapy. Treatment-emergent adverse events (TEAEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 15. Maximum severity and relation to study drug for TEAEs were determined by the investigator. Safety was monitored throughout the study by a safety committee composed of the sponsor's medical monitor and at least one of the study's principal investigators.

Statistical analysis. For all subjects who received at least a partial dose of study drug, descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum) were performed for age, body mass index, and weight. Sex and race were listed and tabulated. Individual and mean doripenem plasma concentration-time profiles were plotted. Plasma and urine doripenem concentrations at each time point and pharmacokinetic parameters were summarized with mean, SD, coefficient of variation, median, minimum, and maximum. Exploratory graphic analysis was performed to evaluate age-related changes in pharmacokinetic parameters.

All subjects who received at least a partial dose of the study drug were included in the safety and tolerability analysis. The percentage of subjects with specific TEAEs was summarized. For clinical laboratory tests, descriptive statistics were calculated for each laboratory analyte at baseline and at each time point. Descriptive statistics were also used to evaluate changes in vital signs (pulse rate, respiratory rate, temperature, and systolic and diastolic blood pressure) at each time point, and physical examination results were listed.

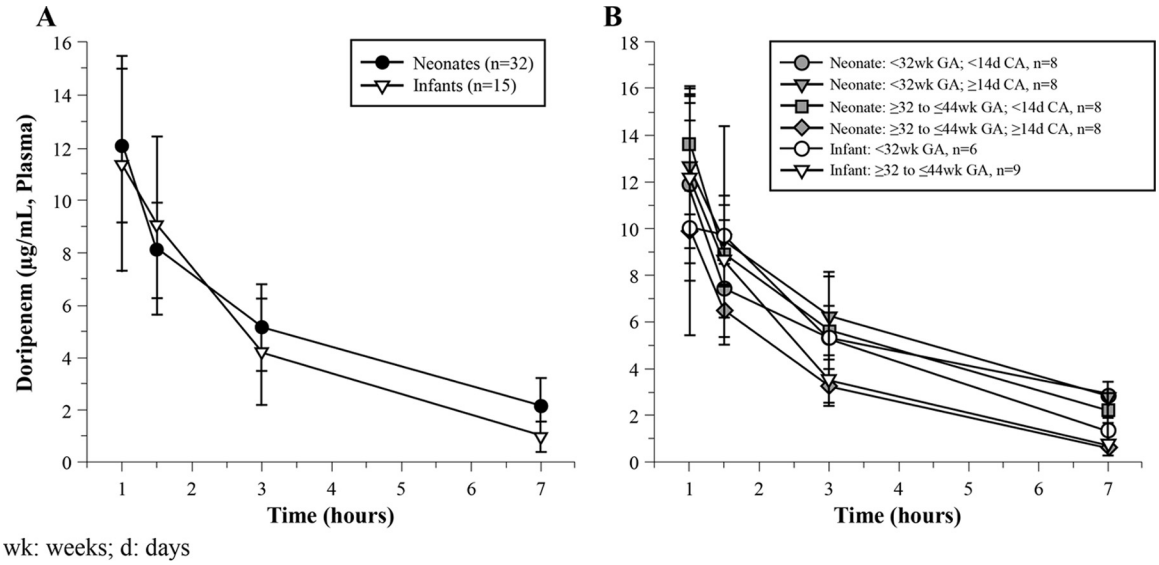

FIG 1 Mean (SD) concentration-time profiles of doripenem per study population and age group. (A) Neonates and infants. (B) Groups 1 to 6.

RESULTS

Baseline characteristics. A total of 52 subjects were assigned to the 6 age groups, of which 51 (98%) completed the study (Table 1). One subject in group 6 (≥32 to ≤44 weeks in GA and 4 to <12 weeks in CA) was withdrawn from the study due to personal reasons (family request/decision). The majority of subjects (n = 43, 83%) were Caucasian with a mean age of 23.2 days (range, 1 to 74 days). Mean baseline weight ± SD was 2.53 ± 1.259 kg. There was a higher percentage of female subjects (54%) than male. Four subjects had preplanned surgeries or procedures that may have affected volumes of distribution. Two in group 2 (<32 weeks in GA and ≥14 days to <4 weeks in CA) had clipping of ductus arteriosus and elective removal of chest tube, 1 in group 4 (≥32 to ≤44 weeks in GA and ≥14 days to <4 weeks in CA) had an incision and drainage procedure for a right upper chest wall abscess, and 1 in group 5 (<32 weeks in GA and 4 to <12 weeks in CA) had patent ductus arteriosus ligation.

Pharmacokinetic results for doripenem. Of the 51 subjects who completed the study, 5 subjects were excluded from all pharmacokinetic assessments: 3 subjects for deviations from protocol-planned doripenem administration, 1 subject due to a required blood transfusion the same day as study drug administration, and

TABLE 2 Arithmetic mean (SD) doripenem plasma pharmacokinetic parameters per study population[a]

Parameter	Neonate (<4 wk in CA), 5 mg/kg	Infant (4 to <12 wk in CA), 5 or 8 mg/kg	Infant (<8 wk in CA), 5 mg/kg	Infant (≥8 wk in CA), 8 mg/kg
n	32	14	10	4
C_{inf} (µg/ml)	12.1 (2.90)	11.4 (4.23)[b]	9.58 (2.70)	16.0 (4.07)
C_{max} (µg/ml)	12.2 (2.70)	11.7 (4.02)[b]	10.0 (2.54)	16.0 (4.07)
t_{max} (h), median (range)	1.00 (0.98–1.50)	1.00 (0.98–1.58)[b]	1.00 (0.98–1.58)	1.00 (1.00–1.07)
AUC_{last} (µg · h/ml)	35.8 (8.95)	32.2 (10.8)[b]	26.7 (5.56)	45.9 (7.79)
AUC_{∞} (µg · h/ml)	45.7 (15.3)[c]	32.4 (9.56)[d]	28.1 (4.87)[e]	45.2 (8.86)[f]
$t_{1/2}$ (h)	2.98 (1.11)[c]	1.79 (0.577)[d]	1.95 (0.580)[e]	1.34 (0.264)[f]
CL/BW (ml/min/kg)	2.08 (0.849)[c]	3.03 (0.455)[d]	3.03 (0.460)[e]	3.02 (0.538)[f]
V_z/BW (liters/kg)	0.474 (0.0956)[c]	0.464 (0.142)[d]	0.504 (0.140)[e]	0.343 (0.0532)[f]
CL_{CR}[i] (ml/min/kg)				
Baseline	21.4 (7.69)[g]	23.6 (8.39)[h]		
End of study	22.0 (7.93)[g]	26.4 (9.14)[h]		

[a] Subjects <8 weeks in CA received doripenem as a 5-mg/kg 1-hour i.v. infusion; subjects ≥8 weeks in CA received doripenem as an 8-mg/kg 1-hour i.v. infusion.
[b] n = 14.
[c] n = 30.
[d] n = 12.
[e] n = 9.
[f] n = 3.
[g] n = 31.
[h] n = 13.
[i] CL_{CR} was calculated using the Schwartz equation.

TABLE 3 Arithmetic mean (SD) doripenem plasma pharmacokinetic parameters per stratification and age group[a]

Parameter	Neonate (<4 wk in CA), 5 mg/kg				Infant (4 to <12 wk in CA): <8 wk in CA, 5 mg/kg, and ≥8 wk in CA, 8 mg/kg	
	<32 wk in GA		≥32 to ≤44 wk in GA			
	<14 days in CA; group 1	≥14 days in CA; group 2	<14 days in CA; group 3	≥14 days in CA; group 4	<32 wk in GA; group 5	≥32 to ≤44 wk in GA; group 6
n	8	8	8	8	6	9
C_{inf} (μg/ml)	11.9 (4.11)	12.7 (2.65)	13.7 (2.03)	9.91 (0.723)	9.90 (5.13)[b]	12.3 (3.71)
C_{max} (μg/ml)	12.2 (3.67)	13.2 (2.12)	13.7 (2.03)	9.91 (0.723)	10.8 (4.83)[b]	12.3 (3.71)
t_{max} (h), median (range)	1.00 (1.00–1.50)	1.00 (1.00–1.50)	1.00 (1.00–1.00)	1.00 (0.98–1.00)	1.00 (1.00–1.58)[b]	1.00 (0.98–1.07)
AUC_{last} (μg · h/ml)	37.2 (5.93)	42.0 (7.72)	39.4 (6.39)	24.6 (3.77)	35.0 (14.8)	30.0 (6.91)[c]
AUC_{∞} (μg · h/ml)	55.3 (10.1)[d]	54.6 (11.7)[d]	49.2 (10.9)	26.2 (4.62)	32.9 (15.1)[e]	32.2 (6.80)[c]
$t_{1/2}$ (h)	4.22 (0.429)[d]	3.40 (0.894)[d]	2.85 (0.641)	1.66 (0.385)	2.03 (0.369)[e]	1.67 (0.644)[c]
CL/BW (ml/min/kg)	1.56 (0.340)[d]	1.59 (0.370)[d]	1.78 (0.434)	3.27 (0.589)	3.07 (0.474)[e]	3.01 (0.476)[c]
V_z/BW (liters/kg)	0.564 (0.0975)[d]	0.455 (0.0859)[d]	0.424 (0.0597)	0.461 (0.0907)	0.548 (0.151)[e]	0.422 (0.125)[c]
CL_{CR}[f] (ml/min/kg)						
Baseline	18.8 (4.98)	28.5 (7.27)[d]	15.1 (5.49)	24.2 (6.44)	29.7 (7.74)	18.4 (4.71)[d]
End of study	17.8 (4.89)	30.3 (6.80)[d]	16.1 (6.07)	24.7 (5.66)	31.2 (10.1)	22.2 (6.15)[d]

[a] Subjects <8 weeks in CA received doripenem as a 5-mg/kg 1-hour i.v. infusion; subjects ≥8 weeks in CA received doripenem as an 8-mg/kg 1-hour i.v. infusion.
[b] $n = 5$.
[c] $n = 8$.
[d] $n = 7$.
[e] $n = 4$.
[f] CL_{CR} was calculated using the Schwartz equation.

1 subject for having too few pharmacokinetic samples for analysis. Dosing errors were not considered to have affected the overall interpretation of study results. Two subjects received less than the planned dose of doripenem (doripenem at 7.10 mg instead of doripenem at 8.35 mg, and doripenem at 0.815 mg instead of doripenem at 8.15 mg), and 2 subjects did not receive the doripenem infusion as stated in the protocol (1 received doripenem over 74 min in place of 60 min). Final pharmacokinetic analysis included data from 46 subjects.

Mean (SD) plasma concentration-time profiles of doripenem were similar in shape for neonates (>4 weeks in CA) and infants (≥4 to <12 weeks in CA), with maximum concentrations occurring at the end of the doripenem infusion (1 h) (Fig. 1A). Mean (SD) plasma concentration-time profiles were also similar across the 6 age groups (Fig. 1B). Five infants were ≥8 weeks in CA at enrollment and therefore received a doripenem 8-mg/kg 1-hour infusion. Most subjects had measurable doripenem concentrations (0.323 to 3.71 μg/ml) 7 h after the start of the infusion (the last scheduled pharmacokinetic sample time point), which were approaching the lower limit of assay detection.

Mean C_{max} and median t_{max} for doripenem were similar when comparing neonates (<4 weeks in CA) and infants (≥4 to <12 weeks in CA) (Table 2); among the 6 age groups, the lowest mean C_{max} (9.9 μg/ml) was in group 4 (neonates ≥32 to ≤44 weeks in GA and ≥14 days to <4 weeks in CA) (Table 3).

Mean doripenem AUC_{last} values were similar across the CA range, but AUC_{∞} was approximately 41% greater in neonates than in infants based on differences in elimination parameters (Table 2). Mean doripenem $t_{1/2}$ was 66% longer (2.98 versus 1.79 h) and clearance normalized for body weight (CL/BW) was 31% lower (2.08 versus 3.03 ml/min/kg) in neonates than in infants. Among infants, mean AUC_{last}, AUC_{∞}, and CL/BW were similar but were more variable in infants born at younger GAs. Among neonates, mean AUC_{last} and AUC_{∞} were approximately 38% and 50% lower, respectively, in the oldest-age neonate group (group 4, ≥32 to ≤44 weeks in GA and ≥14 days to <4 weeks in CA) than in the rest of the neonates (Table 3).

Mean doripenem V_z/BW values were similar between neonates and infants and decreased slightly with CA, but there was no significant trend (Fig. 2). Subjects born at the earliest GA, however, had the largest volumes. The oldest neonate age group (group 4,

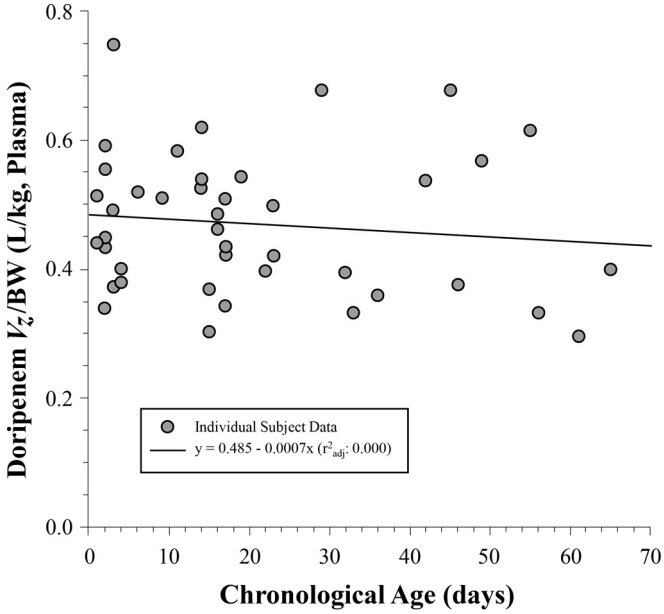

FIG 2 Individual subject doripenem V_z/BW versus CA. A linear regression model was fitted with V_z/BW as the dependent variable and CA as a linear predictor. The slope of the regression line (−0.0007) was found to not be statistically significant ($P = 0.4614$).

TABLE 4 Arithmetic median (range) doripenem time above and percent time above a MIC of 1 μg/ml for an 8-hour dosing interval

Parameter	Neonate (<4 wk in CA)				Infant (4 to <12 wk in CA)	
	<32 wk in GA		≥32 to ≤44 wk in GA			
	<14 days in CA; group 1	≥14 days in CA; group 2	<14 days in CA; group 3	≥14 days in CA; group 4	<32 wk in GA; group 5	≥32 to ≤44 wk in GA; group 6
n	8	8	8	8	6	9
T>MIC (h)	7.91 (7.88–7.93)	7.93 (7.91–7.93)	7.93 (6.92–7.93)	5.57 (4.35–7.51)	7.33 (5.59–7.93)	5.70 (3.63–7.88)
%*T*>MIC	98.8 (98.5–99.1)	99.1 (98.9–99.1)	99.1 (86.5–99.1)	69.6 (54.4–93.9)	91.6 (69.9–99.1)	71.3 (45.4–98.5)

≥32 to ≤44 weeks in GA and ≥14 days to <4 weeks in CA) had mean values similar to those for infants (Table 3). Mean CL_{CR} values were similar between neonates and infants (Table 2). Within the neonate group, CL_{CR} was approximately 50% greater in the neonates ≥14 days in CA than in neonates <14 days in CA regardless of GA at time of birth (Table 3). Creatinine was quantified using enzymatic analytical techniques (30).

In an exploratory analysis, *T*>MIC and %*T*>MIC were calculated based on an 8-hour period (the approved typical doripenem dosing interval in adults). After single-dose administration of doripenem (5 mg/kg [infants <8 weeks] or 8 mg/kg [infants ≥8 weeks]), doripenem concentrations were maintained above a MIC of 1 μg/ml for a median %*T*>MIC of approximately 90% to 100%, except for the oldest neonates (group 4, ≥32 to ≤44 weeks in GA and ≥14 days to <4 weeks in CA) and infants with the longest GA (group 6, ≥32 to ≤44 weeks in GA and 4 to <12 weeks in CA), where the median %*T*>MIC for both groups was approximately 70% (Table 4). Individual %*T*>MIC values ranged from 45.4% to 99.1%.

Safety. There were no deaths reported in the study, and no adverse events led to discontinuation of the study drug. One serious adverse event (sepsis) was reported; it was assessed as severe in intensity and considered not related to study drug by the investigator. In 21 subjects (40.4%), at least 1 TEAE was recorded (Table 5). Most TEAEs were mild to moderate and were resolved by the end of the study. Incidence of TEAEs was higher in group 2 (neonates <32 weeks in GA and ≥14 days to <4 weeks in CA) than in other groups (Table 5); this was likely not clinically relevant and was related to the small sample size in all cohorts. All events were expected to be observed in this subject population. There were no clinically meaningful physical examination findings or changes in mean vital sign parameters reported in the study.

DISCUSSION

In this study, in (pre)term neonates and infants, there was no change in the shape of the doripenem concentration-time profiles in infants compared with those observed in older children and adults, indicating that the general pharmacokinetic disposition of doripenem is similar in infants. The intrasubject variability around exposure parameters was consistent with what has typically been observed with doripenem exposure data in older children and healthy adults (31; Cirillo et al., poster). Doripenem concentration data overlapped in neonates and older infants. Individual data from children 3 months to <18 years obtained from a previously conducted study (Cirillo et al., poster) were plotted with AUC data from infants in this study, where the relation of doripenem AUC_{∞} to CA was evaluated (Fig. 3).

Systemic exposures at doses evaluated in infants (5 or 8 mg/kg) were generally within the range of what has previously been observed in older children and healthy adult subjects administered a single doripenem 500-mg dose over 1 h (approximate mean [SD] AUC_{∞}, 36.3 μg · h/ml [8.77]) (31). The small slope of the relation between doripenem AUC and subject age supports the idea that this target exposure was generally achieved with the administered single doses in infants as well as in older children, noting that AUC_{∞} in neonates <32 weeks in GA was approximately 41%

TABLE 5 Treatment-emergent adverse events[a]

Characteristic	Neonate (<4 wk in CA)				Infant (4 to <12 wk in CA)		
	<32 wk in GA		≥32 to ≤44 weeks GA				
	<14 days in CA; group 1	≥14 days in CA; group 2	<14 days in CA; group 3	≥14 days in CA; group 4	<32 wk in GA; group 5	≥32 to ≤44 wk in GA; group 6	Total
n	8	9	9	8	7	11	52
Subjects with adverse events, *n* (%)	3 (37.5)	7 (77.8)	1 (11.1)	3 (37.5)	4 (57.1)	3 (27.3)	21 (40.4)
Most common adverse events (≥2% of subjects), *n* (%)							
Neonatal anemia	0	3 (33.3)	0	0	1 (14.3)	0	4 (7.7)
Hypoalbuminemia	0	3 (33.3)	0	0	0	0	3 (5.8)
Fungal infection	0	1 (11.1)	0	0	1 (14.3)	0	2 (3.8)
Nosocomial infection	1 (12.5)	1 (11.1)	0	0	0	0	2 (3.8)
Hyperglycemia	1 (12.5)	1 (11.1)	0	0	0	0	2 (3.8)
Peripheral edema	0	1 (11.1)	0	1 (12.5)	0	0	2 (3.8)
Diaper dermatitis	0	0	0	0	1 (14.3)	1 (9.1)	2 (3.8)
Patent ductus arteriosus	2 (25)	0	0	0	0	0	2 (3.8)

[a] Percentages were calculated with the number of subjects in each group as denominator. Incidence is based on number of subjects, not number of events.

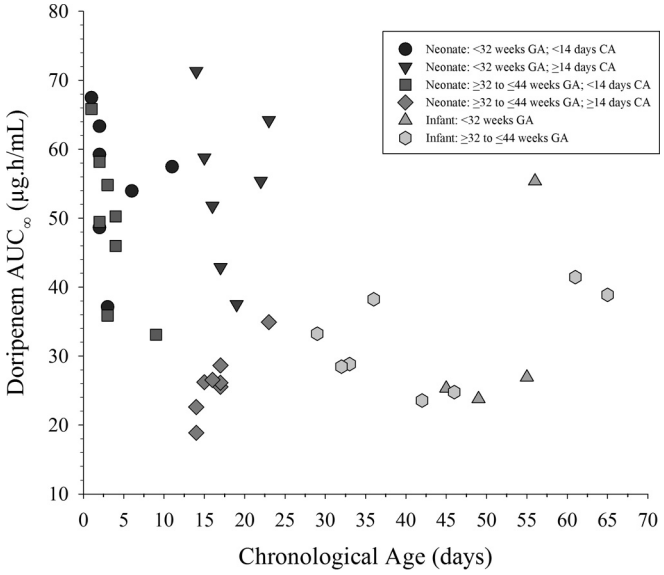

FIG 3 Individual subject doripenem AUC_{∞} versus CA.

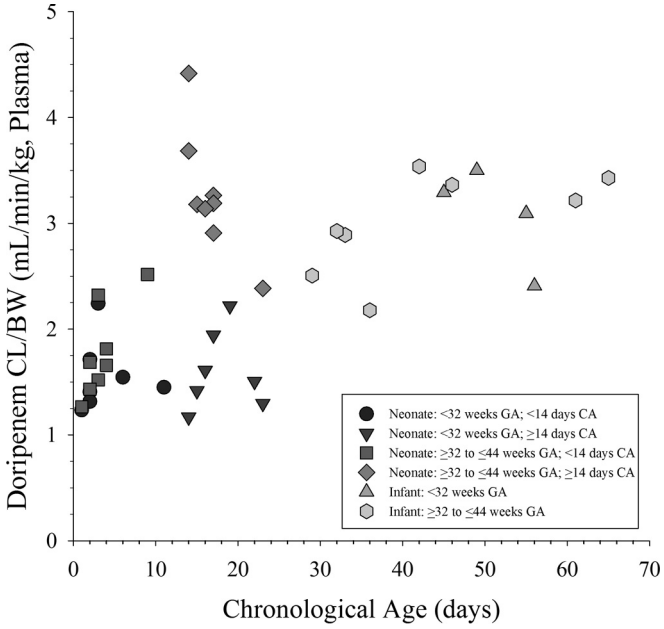

FIG 4 Individual subject doripenem CL/BW versus CA.

greater than in other infants based on differences in elimination parameters, including a longer $t_{1/2}$. As pharmacokinetic and pharmacodynamic properties may differ between preterm and term neonates and age was treated as a continuous variable, data were also summarized to review doripenem pharmacokinetics in subjects <37 weeks in GA (preterm) versus those born ≥37 weeks in GA (term). Data within these groups were generally similar, more so than when compared by a GA cutoff of 32 weeks, presumably due to the impact of renal maturation elements at this earlier developmental stage.

For doripenem, a modest decreasing trend in weight-corrected systemic clearance with increasing age to adolescence was previously noted, with CL values approaching those observed in healthy adult subjects between 15 and 17 years of age (Cirillo et al., poster). To appreciate this change from birth to adulthood, data from infants were plotted with previously collected doripenem data from children <18 years of age, and the relation between doripenem CL/BW and CA was evaluated by fitting a linear regression model to the data (Fig. 4).

Doripenem, like other carbapenems, exhibits time-dependent bactericidal killing measured by %*T*>MIC (32, 33). An exploratory %*T*>MIC was estimated for all age groups over an 8-hour period, the standard dosing interval for doripenem using the respective dose per group of 5 mg/kg (infants <8 weeks) or 8 mg/kg (infants ≥8 weeks). At a target MIC of 1 μg/ml, the median %*T*>MIC was between 70% and 100%. A target MIC of 1 μg/ml was chosen because it represents the upper limit of the MIC distribution for relevant organisms for neonates (11–19). These data can help to inform dose determinations in infants.

One study limitation was that the sample sizes in all cohorts were relatively small (n <12), thus limiting the ability to make definitive conclusions regarding trends in the safety profile of single doses of doripenem in neonates and infants <12 weeks in CA.

In conclusion, doripenem plasma exposures in preterm and term neonates and infants <12 weeks in CA at the doses evaluated in this study (5 mg/kg in infants <8 weeks in CA; 8 mg/kg in infants ≥8 weeks in CA) were generally similar to the exposures achieved with 500-mg doses in infected adults that have been associated with clinical and microbiologic success in treating infections. The systemic exposure in terms of AUC_{∞} generally increased in subjects born at younger GAs along with a slower elimination of doripenem from the systemic circulation. Doripenem administered as a single dose of 5 mg/kg (infants <8 weeks) or 8 mg/kg (infants ≥8 weeks) over a 1-hour infusion in medically stable infants <12 weeks in CA was generally safe and well tolerated in this study.

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