Clinical trial results:
An Open-Label Study to Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Doripenem in Infants (Term and Preterm), Less Than 12 Weeks Chronological Age

Summary

EudraCT number	2009-014387-20
Trial protocol	BE GB Outside EU/EEA
Global end of trial date	30 April 2012

Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	22 July 2015

Trial information

Trial identification

Sponsor protocol code	DORI-PED-1003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01381848
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium,
Public contact	Janssen-Cilag International NV, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen-Cilag International NV, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000015-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 April 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the pharmacokinetics (PK) of doripenem after single-dose administration of doripenem to infants (term and preterm), less than (<) 12 weeks chronological age (CA). Safety and tolerability were also assessed.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Subjects' safety was monitored throughout the study by a safety committee composed of the sponsor's medical monitor and at least 1 of the study's principal investigators. The committee reviewed safety information at least once a month or after every subjects enrolled and dosed. Safety was evaluated by examining incidence, severity, relationship to study drug and types of adverse events, changes in clinical laboratory results (hematology and serum biochemistry), physical examination, vital sign measurements and concomitant therapy.

Background therapy:

All medications were allowed except concomitant use of probenecid valproic acid, and imipenem/cilastatin, which have documented or potential interactions with doripenem.

Evidence for comparator: -

Actual start date of recruitment	19 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 36
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	52
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	34

Infants and toddlers (28 days-23 months)	18
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 19 Nov 2009 to 30 Apr 2012. A total of 52 subjects were assigned to 1 of the 6 age groups, of which 51 (98%) subjects completed the study. One subject was withdrawn from the study due to personal reasons.

Pre-assignment

Screening details:

In this study subjects were enrolled based on CA and categorized into either a neonate or infant age group. Thirty-two neonatal male and female subjects, and 16 infant male and female subjects, were to be included in the study population to ensure that at least 48 subjects complete all required assessments.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Neonates <32 weeks gestational age (GA) and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

Arm type	Experimental
Investigational medicinal product name	DORIBAX
Investigational medicinal product code	
Other name	DORIPENEM HYDRATE
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects >=8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

Arm title	Group 2

Arm description:

Neonates <32 weeks GA and >=14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

Arm type	Experimental
Investigational medicinal product name	DORIBAX
Investigational medicinal product code	
Other name	DORIPENEM HYDRATE
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects >=8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

Arm title	Group 3

Arm description:

Neonates >=32 weeks to <=44 weeks GA and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

Arm type	Experimental
Investigational medicinal product name	DORIBAX
Investigational medicinal product code	
Other name	DORIPENEM HYDRATE
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects >= 8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

Arm title	Group 4

Arm description:

Neonates >=32 weeks to <=44 weeks GA and >=14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

Arm type	Experimental
Investigational medicinal product name	DORIBAX
Investigational medicinal product code	
Other name	DORIPENEM HYDRATE
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects >= 8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

Arm title	Group 5

Arm description:

Infants <32 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day

Arm type	Experimental
Investigational medicinal product name	DORIBAX
Investigational medicinal product code	
Other name	DORIPENEM HYDRATE
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects >= 8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

Arm title	Group 6

Arm description:

Infants >=32 weeks to <=44 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day

Arm type	Experimental
Investigational medicinal product name	DORIBAX
Investigational medicinal product code	
Other name	DORIPENEM HYDRATE
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects >=8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	8	9	9
Completed	8	9	9
Not completed	0	0	0
Other	-	-	-

Number of subjects in period 1	Group 4	Group 5	Group 6
Started	8	7	11
Completed	8	7	10
Not completed	0	0	1
Other	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Neonates <32 weeks gestational age (GA) and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	

Reporting group title	Group 2
Reporting group description:	
Neonates <32 weeks GA and >=14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	

Reporting group title	Group 3
Reporting group description:	
Neonates >=32 weeks to <=44 weeks GA and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 4
Reporting group description:	
Neonates >=32 weeks to <=44 weeks GA and >=14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 5
Reporting group description:	
Infants <32 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 6
Reporting group description:	
Infants >=32 weeks to <=44 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	8	9	9
Title for AgeCategorical			
Units: subjects			
Newborns (0-27 days)	8	9	9
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous			
Units: days			
arithmetic mean	3.6	19	3.7
standard deviation	± 3.34	± 3.61	± 2.35
Title for Gender			
Units: subjects			
Female	4	3	5
Male	4	6	4

Reporting group values	Group 4	Group 5	Group 6
Number of subjects	8	7	11
Title for AgeCategorical			
Units: subjects			
Newborns (0-27 days)	8	0	0
Infants and toddlers (28 days-23 months)	0	7	11
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous			
Units: days			
arithmetic mean	16.6	52	43.2
standard deviation	± 2.88	± 12.99	± 13.6
Title for Gender			
Units: subjects			
Female	5	5	6
Male	3	2	5

Reporting group values	Total		
Number of subjects	52		
Title for AgeCategorical			
Units: subjects			
Newborns (0-27 days)	34		
Infants and toddlers (28 days-23 months)	18		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65 to 84 years	0		
85 years and over	0		
Title for AgeContinuous			
Units: days			
arithmetic mean			
standard deviation	-		
Title for Gender			
Units: subjects			
Female	28		
Male	24		

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description:	
Neonates <32 weeks gestational age (GA) and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	

Reporting group title	Group 2
Reporting group description:	
Neonates <32 weeks GA and >=14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	

Reporting group title	Group 3
Reporting group description:	
Neonates >=32 weeks to <=44 weeks GA and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 4
Reporting group description:	
Neonates >=32 weeks to <=44 weeks GA and >=14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 5
Reporting group description:	
Infants <32 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 6
Reporting group description:	
Infants >=32 weeks to <=44 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day	

Primary: Maximum Observed Plasma Concentration (Cmax) of Doripenem

End point title	Maximum Observed Plasma Concentration (Cmax) of Doripenem[1]
End point description:	
PK analysis was conducted in subjects with at least 1 PK blood sample.	
End point type	Primary
End point timeframe:	
Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: microgram per milliliters (mcg/mL)				
arithmetic mean (standard deviation)	12.2 (± 3.67)	13.2 (± 2.12)	13.7 (± 2.03)	9.91 (± 0.723)

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[2]	9		
Units: microgram per milliliters (mcg/mL)				
arithmetic mean (standard deviation)	10.8 (± 4.83)	12.3 (± 3.71)		

Notes:

[2] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Observed Plasma Concentration at the end of the Doripenem Infusion (Cinf; may or may not be Cmax)

End point title	Observed Plasma Concentration at the end of the Doripenem Infusion (Cinf; may or may not be Cmax)[3]

End point description:

PK analysis was conducted in subjects with at least 1 PK blood sample.

End point type	Primary

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: mcg/mL				
arithmetic mean (standard deviation)	11.9 (± 4.11)	12.7 (± 2.65)	13.7 (± 2.03)	9.91 (± 0.723)

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[4]	9		
Units: mcg/mL				
arithmetic mean (standard deviation)	9.9 (± 5.13)	12.3 (± 3.71)		

Notes:

[4] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Time to reach the Maximum Observed Plasma Concentration (tmax)

End point title	Time to reach the Maximum Observed Plasma Concentration (tmax)[5]

End point description:

PK analysis was conducted in subjects with at least 1 PK blood sample.

End point type	Primary

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: hours (h)				
median (full range (min-max))	1 (1 to 1.5)	1 (1 to 1.5)	1 (1 to 1)	1 (0.98 to 1)

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[6]	9		
Units: hours (h)				
median (full range (min-max))	1 (1 to 1.58)	1 (0.98 to 1.07)		

Notes:

[6] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Area under the Plasma Concentration-Time Curve From Time 0 to C Last (AUClast)

End point title	Area under the Plasma Concentration-Time Curve From Time 0 to C Last (AUClast)[7]

End point description:

Area under the plasma concentration time curve from zero to the last measured concentration (AUClast). PK population included all evaluable subjects who received at least 1 dose of study medication and had sufficient post-dose blood samples to estimate AUClast.

End point type	Primary

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	8
Units: microgram*hour per milliliter (mcg.h/mL)				
arithmetic mean (standard deviation)	37.2 (± 5.93)	42 (± 7.72)	39.4 (± 6.39)	24.6 (± 3.77)

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	8[8]		
Units: microgram*hour per milliliter (mcg.h/mL)				
arithmetic mean (standard deviation)	35 (± 14.8)	30 (± 6.91)		

Notes:

[8] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve From Time 0 to Infinite Time (AUC [0 - infinity])

End point title	Area Under the Plasma Concentration-Time Curve From Time 0 to Infinite Time (AUC [0 - infinity])[9]

End point description:

AUC (0 - infinity) is area under the plasma concentration versus time curve (AUC) from time zero (predose) to extrapolated infinite time (0 - infinity). PK analysis was conducted in subjects with at least 1 PK blood sample.

End point type	Primary

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[10]	7[11]	8	8
Units: mcg.h/mL				
arithmetic mean (standard deviation)	55.3 (± 10.1)	54.6 (± 11.7)	49.2 (± 10.9)	26.2 (± 4.62)

Notes:

[10] - 'N' signifies number of subjects analysed for this end point.

[11] - 'N' signifies number of subjects analysed for this end point.

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[12]	8[13]		
Units: mcg.h/mL				

arithmetic mean (standard deviation)	32.9 (± 15.1)	32.2 (± 6.8)		

Notes:

[12] - 'N' signifies number of subjects analysed for this end point.

[13] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Elimination Half-Life (t1/2)

End point title	Elimination Half-Life (t1/2)[14]

End point description:

Plasma decay half-life is the time measured for the plasma concentration to decrease by one half, associated with the terminal slope (lamda- z) of the semi logarithmic drug concentration-time curve, calculated as 0.693/lamda-z. PK analysis was conducted in subjects with at least 1 PK blood sample.

End point type	Primary

End point timeframe:

Immediately before end of infusion;1.5, 3, 7 hours after end of infusion

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[15]	7[16]	8	8
Units: hours (h)				
arithmetic mean (standard deviation)	4.22 (± 0.429)	3.4 (± 0.894)	2.85 (± 0.641)	1.66 (± 0.385)

Notes:

[15] - 'N' signifies number of subjects analysed for this end point.

[16] - 'N' signifies number of subjects analysed for this end point.

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[17]	8[18]		
Units: hours (h)				
arithmetic mean (standard deviation)	2.03 (± 0.369)	1.67 (± 0.644)		

Notes:

[17] - 'N' signifies number of subjects analysed for this end point.

[18] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Total Clearance of Drug Normalized by Body Weight (CL/BW)

End point title	Total Clearance of Drug Normalized by Body Weight

End point description:

Total clearance of drug after intravenous administration, calculated as: dose/AUC(0-infinity) (for doripenem only). PK analysis was conducted in subjects with at least 1 PK blood sample.

End point type	Primary

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[20]	7[21]	8	8
Units: mL/min/kg				
arithmetic mean (standard deviation)	1.56 (± 0.34)	1.59 (± 0.37)	1.78 (± 0.434)	3.27 (± 0.589)

Notes:

[20] - 'N' signifies number of subjects analysed for this end point.

[21] - 'N' signifies number of subjects analysed for this end point.

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[22]	8[23]		
Units: mL/min/kg				
arithmetic mean (standard deviation)	3.07 (± 0.474)	3.01 (± 0.476)		

Notes:

[22] - 'N' signifies number of subjects analysed for this end point.

[23] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Volume of Distribution Normalized by Body Weight (Vdz)/BW)

End point title	Apparent Volume of Distribution Normalized by Body Weight (Vdz)/BW)[24]

End point description:

Apparent volume of distribution based on the terminal phase, calculated as D/(lamda-z AUC(0-infinity) (for doripenem only). PK analysis was conducted in subjects with at least 1 PK blood sample.

End point type	Primary

End point timeframe:

Immediately before end of infusion;1.5, 3, 7 hours after end of infusion

Notes:

[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[25]	7[26]	8	8
Units: liters per kilogram (L/kg)				
arithmetic mean (standard deviation)	0.564 (± 0.0975)	0.455 (± 0.0859)	0.424 (± 0.0597)	0.461 (± 0.0907)

Notes:

[25] - 'N' signifies number of subjects analysed for this end point.

[26] - 'N' signifies number of subjects analysed for this end point.

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[27]	8[28]		
Units: liters per kilogram (L/kg)				
arithmetic mean (standard deviation)	0.548 (± 0.151)	0.422 (± 0.125)		

Notes:

[27] - 'N' signifies number of subjects analysed for this end point.

[28] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Primary: Creatinine Clearence (CrCL)

End point title	Creatinine Clearence (CrCL)[29]

End point description:

For all subjects, using the Schwartz equation, creatinine (cr) clearance (CrCL) was calculated: k*length(cm)/Cr, where k is a rate constant equal to 0.45 and length (cm) is infact length at the 50th percentile for a subject and Cr is the subjects creatinine concentration in mg/dL. PK analysis was conducted in subjects with at least 1 PK blood sample.

End point type	Primary

End point timeframe:

Immediately before end of infusion;1.5, 3, 7 hours after end of infusion

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical data were not planned to be reported.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	7[30]	8	8
Units: mL/min/kg				
arithmetic mean (standard deviation)				
Baseline	18.8 (± 4.98)	28.5 (± 7.27)	15.1 (± 5.49)	24.2 (± 6.44)
End of study	17.8 (± 4.89)	30.3 (± 6.8)	16.1 (± 6.07)	24.7 (± 5.66)

Notes:

[30] - 'N' signifies number of subjects analysed for this end point.

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7[31]		
Units: mL/min/kg				
arithmetic mean (standard deviation)				
Baseline	29.7 (± 7.74)	18.4 (± 4.71)		
End of study	31.2 (± 10.1)	22.2 (± 6.15)		

Notes:

[31] - 'N' signifies number of subjects analysed for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A Treatment-Emergent Adverse Event (TEAE) is defined as an AE that was new in onset or aggravated in severity or frequency following the start of administration of the study drug and up to Day 7 that were absent before treatment or that worsened relative to pre-treatment state. Safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline Up to day 7

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	9	8
Units: subjects	3	7	1	3

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	11		
Units: subjects	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects Reporting Treatment-Emergent Serious Adverse Events (TESAEs)

End point description:

A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed

significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline Up to day 7

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	9	8
Units: subjects	0	0	0	0

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	11		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hematology and Biochemistry Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Hematology and Biochemistry Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs)

End point description:

Hematology profile included hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count and biochemistry profile included sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN) creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, lactic acid dehydrogenase, albumin, total bilirubin, and alkaline phosphatase. Subjects with abnormal hematology and biochemistry parameters recorded as TEAEs were reported. Safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline up to Day 7

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	9	8
Units: subjects				
Anaemia neonatal	0	3	0	0
Leukocytosis	0	0	0	0
Hypoalbuminaemia	0	3	0	0
Hyperglycaemia	1	1	0	0
Hypokalaemia	0	0	0	1
Hyponatraemia	0	1	0	0

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	11		
Units: subjects				
Anaemia neonatal	1	0		
Leukocytosis	0	1		
Hypoalbuminaemia	0	0		
Hyperglycaemia	0	0		
Hypokalaemia	0	0		
Hyponatraemia	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Physical Examination Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Physical Examination Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs)

End point description:

Physical examinations were conducted at screening and at the end of the study. Body weight was measured only at screening. Safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline up to Day 7

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	9	8
Units: subjects	0	0	0	0

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	11		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects With Abnormal Vital Signs Recorded as Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of subjects With Abnormal Vital Signs Recorded as Treatment-Emergent Adverse Events (TEAEs)

End point description:

Vital sign assessment included blood pressure, radial pulse rate, body temperature (skin probe, rectal, axillary, or other), and respiration rate. Subjects with abnormal vital signs recorded as TEAEs were reported. Safety population included all subjects who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline up to Day 7

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	9	8
Units: subjects	0	0	0	0

End point values	Group 5	Group 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	11		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Day 7	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Neonates <32 weeks GA and <14 days CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 2
Reporting group description:	
Neonates <32 weeks GA and >=14 days to <4 weeks CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 3
Reporting group description:	
Neonates >=32 weeks to <=44 weeks GA and <14 days CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 4
Reporting group description:	
Neonates >=32 weeks to <=44 weeks GA and >=14 days to <4 weeks CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day	
Reporting group title	Group 5
Reporting group description:	
Infants <32 weeks GA and 4 weeks to <12 weeks CA, Doripenem 5 or 8 mg/kg of body weight by 1-hour infusion per day	
Reporting group title	Group 6
Reporting group description:	
Infants >=32 weeks to <=44 weeks GA and 4 weeks to <12 weeks CA, Doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day	

Serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 4	Group 5	Group 6
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Infections and infestations			
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group 1	Group 2	Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	7 / 9 (77.78%)	1 / 9 (11.11%)
Pregnancy, puerperium and perinatal conditions			
Umbilical Granuloma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Drug Tolerance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infusion Site Haematoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Medical Device Complication			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oedema Peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Bronchospasm			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nasal Congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation Neonatal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Investigations			
Cardiac Murmur			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Post Procedural Oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Patent Ductus Arteriosus			
subjects affected / exposed	2 / 8 (25.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia Neonatal			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Gastritis Haemorrhagic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ileus Paralytic			

subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash Erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dermatitis Diaper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Fungal Infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nosocomial Infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Oral Candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory Tract Infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Food Intolerance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 9 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Hypokalaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Group 4	Group 5	Group 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	3 / 7 (42.86%)	3 / 11 (27.27%)
Pregnancy, puerperium and perinatal conditions			
Umbilical Granuloma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Drug Tolerance			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Infusion Site Haematoma			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Medical Device Complication			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Oedema Peripheral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nasal Congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation Neonatal			

subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Investigations			
Cardiac Murmur			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Post Procedural Oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Patent Ductus Arteriosus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia Neonatal			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Gastritis Haemorrhagic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Ileus Paralytic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash Erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dermatitis Diaper			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	1 / 11 (9.09%)
occurrences (all)	0	1	1

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Fungal Infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Nosocomial Infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Oral Candidiasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Respiratory Tract Infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Food Intolerance			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Sample sizes in all cohorts were relatively small (n<12) limiting the ability to draw definitive conclusions in the safety profile of single 5 or 8 mg/kg doses in neonates and infants <12 weeks CA.

Notes: