Clinical trial results:
A Prospective, Randomized, Double-Blind, Multicenter Study to Establish the Safety and Tolerability of Doripenem Compared With Cefepime in Hospitalized Children With Complicated Urinary Tract Infections.

Summary

EudraCT number	2009-015953-18
Trial protocol	LT CZ PL LV DE Outside EU/EEA
Global end of trial date	26 June 2013

Results information

Result version number	v1
This version publication date	06 July 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	DORIPED3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01110408
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, 2340 Beerse, Belgium, Belgium,
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, 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	26 June 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2013
Global end of trial reached?	Yes
Global end of trial date	26 June 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to establish the safety and tolerability profile of doripenem compared with that of cefepime in hospitalized children 3 months to less then 18 years of age with cUTI (complicated Urinary Tract Infection).

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. An Independent Data Monitoring Committee [IDMC] monitored the safety of participants in this study as well as 2 additional Phase 3 pediatric trials being conducted by the Sponsor simultaneously. Safety evaluations included the measurement of vital signs, monitoring of reported adverse effects (AEs), including serious adverse effects (SAEs), concomitant therapy, serum chemistry, hematology assessments, and urinalysis with microscopy.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	09 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	40
EEA total number of subjects	15

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	16
Children (2-11 years)	19
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A minimum of 120 participants were to be randomly assigned to IV doripenem or IV cefepime in this study in approximate 3:1 ratio. 41 participants were enrolled and 40 participants were treated in this study.

Pre-assignment

Screening details:

A total of 41 participants were enrolled and randomized in the study; 30 participants received doripenem and 10 participants received cefepime. One participant in the doripenem treatment group, after being randomized, was excluded from the study due to protocol violation.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Doripenem

Arm description:

Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 mg/dose) was administered every 8 hours as 60-minutes intravenous [IV] (at least 3 days of IV doripenem only or IV doripenem followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.

Arm type	Experimental
Investigational medicinal product name	Doripenem
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 milligram per dose[mg/dose]) will be administered every 8 hours as 60-minutes intravenous [IV] (at least 3 days of IV doripenem only or IV (at least 3 days of IV doripenem only or IV doripenem followed by oral amoxicillin/clavulanate potassium or ciprofloxacin).

Arm title	Cefepime

Arm description:

Cefepime 50 milligram per kilogram [mg/kg] per dose (up to 2 gram per dose [g/dose]) was administered every 8 hours as 30-minutes intravenous [IV] (atleast 3 days of IV cefepime only or IV cefepime followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.

Arm type	Active comparator
Investigational medicinal product name	Cefepime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cefepime 50 milligram per kilogram (mg/kg) per dose (up to 2 gram per dose g/dose) will be administered every 8 hours as 30 minutes intravenous (at least 3 day of intravenous IV cefepime only or IV cefepime followed by oral amoxicillin/ clavulanate potassium or ciprofloxacin).

Number of subjects in period 1	Doripenem	Cefepime
Started	30	10
Completed	30	10

Baseline characteristics

Reporting groups	
Reporting group title	Doripenem
Reporting group description:	
Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 mg/dose) was administered every 8 hours as 60-minutes intravenous [IV] (at least 3 days of IV doripenem only or IV doripenem followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.	
Reporting group title	Cefepime
Reporting group description:	
Cefepime 50 milligram per kilogram [mg/kg] per dose (up to 2 gram per dose [g/dose]) was administered every 8 hours as 30-minutes intravenous [IV] (atleast 3 days of IV cefepime only or IV cefepime followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.	

Reporting group values	Doripenem	Cefepime	Total
Number of subjects	30	10	40
Title for AgeCategorical			
Units: subjects			
Infants and toddlers (28 days-23 months)	12	4	16
Children (2-11 years)	14	5	19
Adolescents (12-17 years)	4	1	5
Title for AgeContinuous			
Units: years			
arithmetic mean	4.6	4.3	
standard deviation	± 5.22	± 4.16	-
Title for Gender			
Units: subjects			
Female	26	5	31
Male	4	5	9

End points

End points reporting groups

Reporting group title	Doripenem

Reporting group description:

Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 mg/dose) was administered every 8 hours as 60-minutes intravenous [IV] (at least 3 days of IV doripenem only or IV doripenem followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.

Reporting group title	Cefepime

Reporting group description:

Cefepime 50 milligram per kilogram [mg/kg] per dose (up to 2 gram per dose [g/dose]) was administered every 8 hours as 30-minutes intravenous [IV] (atleast 3 days of IV cefepime only or IV cefepime followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.

Subject analysis set title	Clinical Intent-to-Treat (CITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized participants who met the minimal disease definition of complicated urinary tract infection regardless if a baseline pathogen was isolated from the pretreatment urine culture.

Subject analysis set title	Microbiological intent-to-treat (MITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants of all CITT with at least 1 baseline bacterial pathogen isolated from the pretreatment urine culture, susceptible to both doripenem and cefepime. 6 and 2 participants from doripenem and cefepime, respectively had no susceptible urine pathogens at baseline and were excluded from this set.

Primary: The Number of Participants With Clinical Cure Rate at Test Of Cure (TOC) Visit

End point title	The Number of Participants With Clinical Cure Rate at Test Of Cure (TOC) Visit

End point description:

The participants were classified as cure if they had resolution or clinical improvement in signs and symptoms of complicated urinary tract infection; had no fever; no additional antimicrobial therapy was required for the treatment of the infection; and a clinical response assessment of improvement at End of IV visit.

End point type	Primary

End point timeframe:

TOC (7 to 14 days after the last dose of study medication therapy)

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[1]	10[2]		
Units: Participants				
number (not applicable)	20	5		

Notes:

[1] - Clinical Intent-To-Treat

[2] - Clinical Intent-To-Treat

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Doripenem v Cefepime
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Difference clinical cure rates (%)
Point estimate	16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.3
upper limit	58.6

Notes:

[3] - Descriptive study.

Secondary: The Number of Participants With Clinical Improvement Rate at End of IV (EIV) Visit

End point title	The Number of Participants With Clinical Improvement Rate at End of IV (EIV) Visit

End point description:

The participants were considered as clinical improved if they had clinical improvement in signs and symptoms from baseline; no fever for at least the 24 hours before discontinuing the IV study drug; and not received nonstudy antibiotics for the treatment of urinary tract infection after IV study drug therapy had begun.

End point type	Secondary

End point timeframe:

EIV (within 24 hours after completion of the last dose of IV study medication therapy)

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[4]	10[5]		
Units: Participants				
number (not applicable)	28	10		

Notes:

[4] - Clinical Intent-To-Treat

[5] - Clinical Intent-To-Treat

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Doripenem v Cefepime
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Diff. clinical improvement rates (%)
Point estimate	-6.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.3
upper limit	8.9

Notes:

[6] - Descriptive study.

Secondary: The Number of Participants With Clinical Cure Rate at Late Follow-Up (LFU) Visit

End point title	The Number of Participants With Clinical Cure Rate at Late Follow-Up (LFU) Visit

End point description:

The participants were classified as clinical cure if all pretreatment signs and symptoms of complicated urinary tract infection showed no evidence of recurrence after test of cure.

End point type	Secondary

End point timeframe:

LFU (28 to 42 days after the last dose of study medication therapy)

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[7]	10[8]		
Units: Participants				
number (not applicable)	18	5		

Notes:

[7] - Clinical Intent-To-Treat

[8] - Clinical Intent-To-Treat

Statistical analyses

Statistical analysis title	Statistical analysis 3
Comparison groups	Doripenem v Cefepime
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Difference clinical cure rates (%)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.3
upper limit	52.3

Notes:

[9] - Descriptive study

Secondary: The Number of Participants With Favorable Per-participant Microbiological Response

End point title	The Number of Participants With Favorable Per-participant Microbiological Response

End point description:

Favourable per-participant microbiological response rate was evaluated at the at End of IV (EIV) visit, Test Of Cure (TOC) visit, and Late Follow-Up (LFU) visit. The favourable per-participant microbiological response was considered when all baseline pathogens were eradicated (absence) or presumed eradicated (absence of material to culture in a participant who has a positive clinical response to treatment).

End point type	Secondary

End point timeframe:

EIV (within 24 hours after completion of the last dose of IV study medication therapy), TOC (7 to 14 days after the last dose of study medication therapy), and LFU (28 to 42 days after the last dose of study medication therapy)

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[10]	8[11]		
Units: participants				
number (not applicable)				
EIV visit	24	8		
TOC visit	19	4		
LFU visit	16	4		

Notes:

[10] - Microbiological intent-to-treat

[11] - Microbiological intent-to-treat

Statistical analyses

Statistical analysis title	Favorable Microbiological Response (MR) at TOC
Comparison groups	Doripenem v Cefepime
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Difference MR Rate (%)
Point estimate	29.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.4
upper limit	75.8

Notes:

[12] - Descriptive study

Statistical analysis title	Favorable Microbiological Response (MR) at LFU
Comparison groups	Doripenem v Cefepime
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Difference MR Rate (%)
Point estimate	16.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.1
upper limit	64.4

Notes:

[13] - Descriptive study

Secondary: Number of Participants With Favorable Per-pathogen Microbiological Outcome Rate at End of IV (EIV) Visit

End point title	Number of Participants With Favorable Per-pathogen Microbiological Outcome Rate at End of IV (EIV) Visit

End point description:

The favourable per-pathogen microbiological outcome was considered when all baseline pathogens were eradicated (absence) or presumed eradicated (absence of material to culture in a participant who has a positive clinical response to treatment).A total of 4 pathogens in the doripenem group and 2 pathogens in the cefepime group were isolated at baseline from urine culture and were susceptible to the study drug received (see listed in the table below; the numbers in parenthesis next to each pathogen represent the number of participants with the pathogen isolated at baseline in the doripenem and cefepime treatment groups, respectively).

End point type	Secondary

End point timeframe:

EIV (within 24 hours after completion of the last dose of IV study medication therapy)

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[14]	8[15]		
Units: Participants				
number (not applicable)				
Staphylococcus aureus (n=3, 0)	3	0		
Escherichia coli (n=22, 7)	22	7		
Klebsiella oxytoca (n=1, 0)	1	0		
Klebsiella pneumoniae (n=1, 1)	1	1		

Notes:

[14] - Microbiological intent-to-treat

[15] - Microbiological intent-to-treat

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Favorable Per-pathogen Microbiological Outcome Rate at Test Of Cure (TOC) Visit

End point title	Number of Participants With Favorable Per-pathogen Microbiological Outcome Rate at Test Of Cure (TOC) Visit

End point description:

The favourable per-pathogen microbiological outcome was considered when all baseline pathogens were eradicated (absence) or presumed eradicated (absence of material to culture in a participant who has a positive clinical response to treatment). A total of 4 pathogens in the doripenem group and 2 pathogens in the cefepime group were isolated at baseline from urine culture and were susceptible to the study drug received (see listed in the table below; the numbers in parenthesis next to each pathogen represent the number of participants with the pathogen isolated at baseline in the doripenem and

cefepime treatment groups, respectively).

End point type	Secondary

End point timeframe:

TOC (7 to 14 days after the last dose of study medication therapy)

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[16]	8[17]		
Units: Participants				
number (not applicable)				
Staphylococcus aureus (n=3, 0)	3	0		
Escherichia coli (n=22, 7)	17	4		
Klebsiella oxytoca (n=1, 0)	1	0		
Klebsiella pneumoniae (n=1, 1)	1	0		

Notes:

[16] - Microbiological intent-to-treat

[17] - Microbiological intent-to-treat

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Sustained Favorable Per-pathogen Microbiological Outcome Rate at Late Follow-Up (LFU) Visit

End point title	Number of Participants With Sustained Favorable Per-pathogen Microbiological Outcome Rate at Late Follow-Up (LFU) Visit

End point description:

The sustained favourable per-pathogen microbiological outcome was considered when all baseline pathogens were eradicated (absence) or presumed eradicated (absence of material to culture in a participant who has a positive clinical response to treatment). A total of 4 pathogens in the doripenem group and 2 pathogens in the cefepime group were isolated at baseline from urine culture and were susceptible to the study drug received (see listed in the table below; the numbers in parenthesis next to each pathogen represent the number of participants with the pathogen isolated at baseline in the doripenem and cefepime treatment groups, respectively).

End point type	Secondary

End point timeframe:

LFU (28 to 42 days after the last dose of study medication therapy)

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[18]	8[19]		
Units: Participants				
number (not applicable)				
Staphylococcus aureus (n= 3, 0)	2	0		
Escherichia coli (n= 22, 7)	14	4		
Klebsiella oxytoca (n= 1, 0)	1	0		
Klebsiella pneumoniae (n= 1, 1)	1	0		

Notes:
[18] - Microbiological intent-to-treat
[19] - Microbiological intent-to-treat

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Cefepime

Reporting group description:

Cefepime 50 milligram per kilogram [mg/kg] per dose (up to 2 gram per dose [g/dose]) was administered every 8 hours as 30-minutes intravenous [IV] (atleast 3 days of IV cefepime only or IV cefepime followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.

Reporting group title	Doripenem

Reporting group description:

Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 mg/dose) was administered every 8 hours as 60-minutes intravenous [IV] (at least 3 days of IV doripenem only or IV doripenem followed by oral amoxicillin/clavulanate potassium or ciprofloxacin). Total duration of treatment 10 to 14 days.

Serious adverse events	Cefepime	Doripenem	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	1 / 30 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Renal and urinary disorders			
Pyuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pseudomembranous Colitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary Tract Infection			
subjects affected / exposed	2 / 10 (20.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Cefepime	Doripenem	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	16 / 30 (53.33%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Infusion Site Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Irritability			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 30 (10.00%)	
occurrences (all)	1	8	
Vessel Puncture Site Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Productive Cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			

subjects affected / exposed	0 / 10 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Basophil Count Increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Platelet Count Decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Urine Leukocyte Esterase			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Congenital Thrombocyte Disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Myoclonus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Eosinophilia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Hypochromic Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Neutrophilia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Oral Disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed	0 / 10 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Jaundice			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Macule			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Papule			
subjects affected / exposed	1 / 10 (10.00%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Skin Haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Crystalluria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Leukocyturia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Proteinuria			

subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Anal Candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Bacteriuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Fungal Infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Oral Candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Urinary Tract Infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Varicella			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 30 (3.33%) 1	
Metabolism and nutrition disorders Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypoproteinaemia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1 0 / 10 (0.00%) 0	 0 / 30 (0.00%) 0 1 / 30 (3.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2011	The overall reason for the amendment is to incorporate comments from regulatory authorities and investigators from around the world and update the dosing of amoxicillin/clavulanate potassium to every 12 hours [q12h] (7:1 amoxicillin/clavulanate ratio). Inclusion criteria changes included: the requirement of the presence of urine nitrite and leukocyte esterase by urinalysis at baseline. Clarification of the acceptable methods of urine collection as well as to include further investigation to the possible causes contributing to treatment failure. The amendment also update the precautions for medications administered. As well as includes to specify allowable collection methods for urinalysis and microscopy safety assessments. The amendment also includes the requirement that urinalysis with microscopy and creatinine clearance be calculated at baseline as well as to specify time points for the collection of safety laboratory test. It also includes to align the protocol with the EU pediatric investigational plan (PIP) and to remove details of the IDMC that will be specified in the IDMC charter. The amended protocol includes to revise the pharmacokinetic sample collection and handling methods.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 June 2013	This study was terminated early due to business reasons and not related to safety concerns or issues. NOTE: Interruption date indicates the date on which IDMC was notified of premature termination of trial.	-

Notes:

Limitations and caveats

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

The major limitation of the study was limited enrollment which precludes a meaningful conclusion about the efficacy and safety of doripenem compared with cefepime.

Notes: