

**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 Bacterial Pneumonia.**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2009-016069-27
Trial protocol	LT LV Outside EU/EEA
Global end of trial date	21 March 2012

Results information

Result version number	v2 (current)
This version publication date	09 June 2016
First version publication date	23 July 2015
Version creation reason	• Correction of full data set Review of data

Trial information**Trial identification**

Sponsor protocol code	DORIPED3003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01110421
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	21 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2012
Global end of trial reached?	Yes
Global end of trial date	21 March 2012
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 of doripenem compared with that of cefepime in hospitalized children 3 months to less than 18 years of age with suspected bacterial pneumonia including NP (Nosocomial Pneumonia), VAP (Ventilator-Associated Pneumonia), and severe CAP (Community-Acquired Pneumonia).

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	01 December 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	Colombia: 2
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Ukraine: 1
Worldwide total number of subjects	7
EEA total number of subjects	4

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)	0
Children (2-11 years)	7
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:

The study was planned to enroll a minimum of 120 participants but since it was terminated early (05 August 2013), only 7 participants were enrolled in this study at 1 center each in Poland, Ukraine, and Colombia.

Pre-assignment

Screening details:

A total of 7 participants (5 subjects in doripenem group and 2 subjects in cefepime group) were enrolled in this study.

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 milligram per dose [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]) 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).

Arm title	Cefepime
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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] (at least 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]) was administered every 8 hours as 30-minutes intravenous [IV] (at least 3 days of IV cefepime only or IV cefepime followed by oral amoxicillin/clavulanate potassium or ciprofloxacin).

Number of subjects in period 1	Doripenem	Cefepime
Started	5	2
Completed	4	2
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Doripenem
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Reporting group description:

Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 milligram per dose [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
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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] (at least 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	5	2	7
Title for AgeCategorical Units: subjects			
Children (2-11 years)	5	2	7
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: years			
arithmetic mean	5.2	4.5	
standard deviation	± 2.49	± 0.71	-
Title for Gender Units: subjects			
Female	0	1	1
Male	5	1	6

End points

End points reporting groups

Reporting group title	Doripenem
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Reporting group description:

Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 milligram per dose [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
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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] (at least 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)
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All randomized participants who met the minimal disease definition of pneumonia regardless if a baseline pathogen was isolated from the baseline lower respiratory tract culture, pleural fluid or blood culture.

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

Participants of CITT with at least one baseline pneumonia pathogen from pleural fluid, LRT, or blood culture susceptible to doripenem and cefepime. 3 and 2 participants from doripenem and cefepime, respectively had no susceptible pneumonia 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 ^[1]
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End point description:

The participants were classified as cure if they had resolution or clinical improvement of signs and symptoms of pneumonia, favorable response at End of treatment for IV study (EIV) visit; had no fever; improvement or no progression of radiographic findings of pneumonia on chest X ray; improvement in oxygenation or discontinued mechanical ventilation in intubated participants; and not received nonstudy systemic antibacterial therapy for pneumonia.

End point type	Primary
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End point timeframe:

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

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: Descriptive statistics were done, no inferential statistical analyses were performed

End point values	Doripenem	Cefepime		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[2]	2 ^[3]		
Units: Participants				
number (not applicable)	3	2		

Notes:

[2] - Clinical intent-to-treat

[3] - Clinical intent-to-treat

Statistical analyses

No statistical analyses for this end point

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
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End point description:

Participants were considered as clinical improved if they had no fever, clinical improvement in signs and symptoms of pneumonia from baseline, decrease in WBC, improvement or lack of progression of radiographic findings in comparison with the screening chest X-ray, and not received any nonstudy systemic antibacterial therapy for the treatment of pneumonia after IV study drug therapy had begun.

End point type	Secondary
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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	5 ^[4]	2 ^[5]		
Units: Participants				
number (not applicable)	4	2		

Notes:

[4] - Clinical intent-to-treat

[5] - Clinical intent-to-treat

Statistical analyses

No statistical analyses for this end point

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
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End point description:

The participants were classified as clinical cure if all pretreatment signs and symptoms showed no evidence of resurgence after administration of the last dose of study medication and no nonstudy systemic antibacterial therapy was given for the treatment of pneumonia.

End point type	Secondary
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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	5 ^[6]	2 ^[7]		
Units: Participants				
number (not applicable)	3	2		

Notes:

[6] - Clinical intent-to-treat

[7] - Clinical intent-to-treat

Statistical analyses

No statistical analyses for this end point

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

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

Favorable 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 favorable 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). NOTE: No participants in the cefepime treatment group met criteria for inclusion in the Microbiological intent-to-treat analysis.

End point type	Secondary
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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	2 ^[8]	0 ^[9]		
Units: Participants				
number (not applicable)				
TOC visit	2			
EIV visit	2			
LFU visit	2			

Notes:

[8] - MITT

[9] - 1) MITT

2) Participants had no susceptible pneumonia pathogens at baseline and were excluded

Statistical analyses

No statistical analyses for this end point

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
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End point description:

A total of 3 pathogens were isolated at baseline from lower respiratory tract (LRT) culture in 2 participants in the doripenem treatment group and were susceptible to the study drug received: 2 pathogens (Staphylococcus aureus Klebsiella pneumoniae) were isolated at baseline from 1 participant

and a 3rd pathogen (*Streptococcus pneumoniae*) was isolated at baseline from the other participant (see listed in the table below; the number in parenthesis next to each pathogen represent the number of participants with the pathogen isolated at baseline in the doripenem treatment group). 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). NOTE: No participants in the cefepime treatment group met criteria for inclusion in the Microbiological intent-to-treat analysis.

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	2 ^[10]	0 ^[11]		
Units: Participants				
number (not applicable)				
Staphylococcus aureus (n=1)	1			
Streptococcus pneumoniae (n=1)	1			
Klebsiella pneumoniae (n=1)	1			

Notes:

[10] - MITT

[11] - 1) MITT

2) Participants had no susceptible pneumonia pathogens at baseline and were excluded.

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
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End point description:

A total of 3 pathogens were isolated at baseline from lower respiratory tract (LRT) culture in 2 participants in the doripenem treatment group and were susceptible to the study drug received: 2 pathogens (*Staphylococcus aureus* *Klebsiella pneumoniae*) were isolated at baseline from 1 participant and a 3rd pathogen (*Streptococcus pneumoniae*) was isolated at baseline from the other participant (see listed in the table below; the number in parenthesis next to each pathogen represent the number of participants with the pathogen isolated at baseline in the doripenem treatment group). 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). NOTE: No participants in the cefepime treatment group met criteria for inclusion in the Microbiological intent-to-treat analysis.

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	2 ^[12]	0 ^[13]		
Units: Participants				
number (not applicable)				
Staphylococcus aureus (n=1)	1			
Streptococcus pneumoniae (n=1)	1			
Klebsiella pneumoniae (n=1)	1			

Notes:

[12] - MITT

[13] - 1) MITT

2) Participants had no susceptible pneumonia pathogens at baseline and were excluded.

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
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End point description:

A total of 3 pathogens were isolated at baseline from lower respiratory tract (LRT) culture in 2 participants in the doripenem treatment group and were susceptible to the study drug received: 2 pathogens (Staphylococcus aureus Klebsiella pneumoniae) were isolated at baseline from 1 participant and a 3rd pathogen (Streptococcus pneumoniae) was isolated at baseline from the other participant (see listed in the table below; the number in parenthesis next to each pathogen represent the number of participants with the pathogen isolated at baseline in the doripenem treatment group). The favorable 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). NOTE: No participants in the cefepime treatment group met criteria for inclusion in the Microbiological intent-to-treat analysis.

End point type	Secondary
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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	2 ^[14]	0 ^[15]		
Units: Participants				
number (not applicable)				
Staphylococcus aureus (n=1)	1			
Streptococcus pneumoniae (n=1)	1			
Klebsiella pneumoniae (n=1)	1			

Notes:

[14] - MITT

[15] - 1) MITT

2) Participants had no susceptible pneumonia pathogens at baseline and were excluded.

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Doripenem
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Reporting group description:

Doripenem 20 milligram per kilogram [mg/kg] per dose (up to 500 milligram per dose [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
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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] (at least 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

Serious adverse events	Doripenem	Cefepime	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Empyema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Doripenem	Cefepime	
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 5 (60.00%)	1 / 2 (50.00%)	
Investigations Oxygen Saturation Decreased subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 2 (0.00%) 0	
Injury, poisoning and procedural complications Stab Wound subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 2 (0.00%) 0	
General disorders and administration site conditions Chest Pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 2 (0.00%) 0	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 2 (0.00%) 0	
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all) Abdominal Pain Upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 1 / 5 (20.00%) 1 1 / 5 (20.00%) 1	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Acute Respiratory Distress Syndrome subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 1 / 5 (20.00%) 1	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0	
Skin and subcutaneous tissue disorders			

Ecchymosis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 2 (0.00%) 0	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 2 (0.00%) 0	
Musculoskeletal and connective tissue disorders Flank Pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 2 (0.00%) 0	
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1 0 / 5 (0.00%) 0	0 / 2 (0.00%) 0 1 / 2 (50.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 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 every 12 hours [q12h] (7:1 amoxicillin/clavulanate ratio). It includes the clarifications for the doripenem phase 3 program also to clarify that subjects should not receive non study systemic antibacterial therapy for more than 24 hours before the first dose of study drug and to remove CPIS from the study since it has not been validated as a criterion of improvement for children on mechanical ventilation. 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. The amendment incorporate to allow subjects to continue adjunctive therapy when switched to oral medication and to update the dosing of amoxicillin/clavulanate potassium. 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
13 February 2012	On 13 February 2012, the FDA placed the DORIPED3003 Study on clinical hold until after they were able to fully review the "DORINOS3008" final clinical study report and assure the patient population to be enrolled in this trial was not placed under undue risk. At the time the trial was terminated, the clinical hold had not been lifted. In addition, the Paediatric Committee (PDCO) requested that, before the trial DORIPED-3003 can be restarted, the doripenem dosing to be used in this trial be agreed by the PDCO based on providing the full assessment of the adult study DORI-NOS-3008. Trial was terminated prior to this occurring.	-

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: