Clinical trial results:
An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged 3 Months to Twenty-Four Months Who Are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Bacterial Infection Including Peri-Operative Prophylactic Use of Antibiotics

Summary

EudraCT number	2015-002779-64
Trial protocol	Outside EU/EEA
Global end of trial date	20 March 2012

Results information

Result version number	v1
This version publication date	20 April 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	DAP-PEDS-09-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01019395
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cubist Pharmaceuticals
Sponsor organisation address	65 Hayden Avenue, Lexington, United States, 02421
Public contact	Study Director, Cubist Pharmaceuticals, +1 781-860-8660,
Scientific contact	Study Director, Cubist Pharmaceuticals, +1 781-860-8660,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2012
Global end of trial reached?	Yes
Global end of trial date	20 March 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 single dose pharmacokinetics (PK) data of intravenous (i.v.) daptomycin administered at 4 milligrams per kilogram (mg/kg) or 6 mg/kg as a 30 minute infusion in pediatric subjects aged 3 to 24 months, inclusive, with proven or suspected bacterial infection who were receiving standard antibiotic therapy, including subjects that were receiving prophylactic antibiotics peri-operatively.

Protection of trial subjects:

This open-label study did not employ any blinding methods. Screening assessments included medical and medication history, demographics, physical examination, vital signs, a brief neurology examination, electrocardiogram, clinical laboratory tests (hematology, chemistry, urinalysis, serum creatine kinase, and serum creatinine). Study subjects were monitored for adverse events. The study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practices (GCP), Food and Drug Administration (FDA) Code of Federal Regulations (CFR) 312.120, and applicable local regulatory requirements. The protocol, informed consent form (ICF), and all other written documents provided to the parent (or appropriate legal representative) were reviewed and approved by an independent Institutional Review Board (IRB) at each site before the study began. In addition, this study enrolled in a stepwise fashion. It began with age group 1 and after review of PK and safety data, age group 2 was enrolled, and continued in this manner.

Background therapy: -

Evidence for comparator:

This was a non-comparative study.

Actual start date of recruitment	13 January 2010
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	United States: 32
Worldwide total number of subjects	32
EEA total number of subjects	0

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)	32
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: -

Pre-assignment

Screening details:

Written parental (or appropriate legal representative) informed consent was obtained prior to the initiation of any of the assessments/procedures required by the protocol, and subjects met all of the inclusion and none of the exclusion criteria prior to enrollment in this study. Eligible subjects received open-label study drug treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Daptomycin 6 mg/kg: Ages 13 months to 24 months

Arm description:

Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.

Arm type	Experimental
Investigational medicinal product name	Daptomycin
Investigational medicinal product code	
Other name	Cubicin®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

All subjects received a single-dose of daptomycin 6 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 30 minutes. The dosing volume was 25 millilitres (mL) and the infusion rate was 0.83 mL per minute for the 30 minute infusion.

Arm title	Daptomycin 4 mg/kg: Ages 7 months to 12 months

Arm description:

Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

Arm type	Experimental
Investigational medicinal product name	Daptomycin
Investigational medicinal product code	
Other name	Cubicin®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

All subjects received a single-dose of daptomycin 4 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 30 minutes. The dosing volume was 25 mL and the infusion rate was 0.83 mL per minute for the 30 minute infusion.

Arm title	Daptomycin 4 mg/kg: Ages 3 months to 6 months

Arm description:

Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

Arm type	Experimental

Investigational medicinal product name	Daptomycin
Investigational medicinal product code	
Other name	Cubicin®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

All subjects received a single-dose of daptomycin 4 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 30 minutes. The dosing volume was 25 mL and the infusion rate was 0.83 mL per minute for the 30 minute infusion.

Number of subjects in period 1	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months
Started	13	9	10
Subjects that received a complete dose	7	8	9
Completed	7	7	9
Not completed	6	2	1
Not Specified	4	1	-
Parent's Decision	2	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Daptomycin 6 mg/kg: Ages 13 months to 24 months
Reporting group description:	
Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.	
Reporting group title	Daptomycin 4 mg/kg: Ages 7 months to 12 months
Reporting group description:	
Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	
Reporting group title	Daptomycin 4 mg/kg: Ages 3 months to 6 months
Reporting group description:	
Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	

Reporting group values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months
Number of subjects	13	9	10
Age categorical			
Age of all enrolled subjects and all subjects that received a complete dose of study drug.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	13	9	10
Age continuous			
Age of all subjects that received a complete dose of study drug presented. Age of all enrolled subjects was not calculated and values of "0" were presented.			
Units: months			
arithmetic mean	0	0	0
standard deviation	± 0	± 0	± 0
Gender categorical			
Gender of all subjects that received a complete dose of study drug is presented. Gender was not known for 8 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations.			
Units: Subjects			
Female	3	4	8
Male	10	5	2

Reporting group values	Total		
Number of subjects	32		
Age categorical			
Age of all enrolled subjects and all subjects that received a complete dose of study drug.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	32		
Age continuous			
Age of all subjects that received a complete dose of study drug presented. Age of all enrolled subjects was not calculated and values of "0" were presented.			
Units: months			
arithmetic mean			
standard deviation	-		

Gender categorical			
Gender of all subjects that received a complete dose of study drug is presented. Gender was not known for 8 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations.			
Units: Subjects			
Female	15		
Male	17		

Subject analysis sets

Subject analysis set title	Daptomycin 6 mg/kg: Ages 13 to 24 months - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.

Subject analysis set title	Daptomycin 4 mg/kg: Ages 7 to 12 months - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

Subject analysis set title	Daptomycin 4 mg/kg: Ages 3 to 6 months - Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

Reporting group values	Daptomycin 6 mg/kg: Ages 13 to 24 months - Safety Population	Daptomycin 4 mg/kg: Ages 7 to 12 months - Safety Population	Daptomycin 4 mg/kg: Ages 3 to 6 months - Safety Population
Number of subjects	7	8	9
Age categorical			
Age of all enrolled subjects and all subjects that received a complete dose of study drug.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	7	8	9
Age continuous			
Age of all subjects that received a complete dose of study drug presented. Age of all enrolled subjects was not calculated and values of "0" were presented.			
Units: months			
arithmetic mean	19.46	9.8	4.79
standard deviation	± 1.459	± 1.708	± 1.374
Gender categorical			
Gender of all subjects that received a complete dose of study drug is presented. Gender was not known for 8 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations.			
Units: Subjects			
Female	3	4	9
Male	4	4	1

End points

End points reporting groups

Reporting group title	Daptomycin 6 mg/kg: Ages 13 months to 24 months
Reporting group description:	
Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.	
Reporting group title	Daptomycin 4 mg/kg: Ages 7 months to 12 months
Reporting group description:	
Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	
Reporting group title	Daptomycin 4 mg/kg: Ages 3 months to 6 months
Reporting group description:	
Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	
Subject analysis set title	Daptomycin 6 mg/kg: Ages 13 to 24 months - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.	
Subject analysis set title	Daptomycin 4 mg/kg: Ages 7 to 12 months - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	
Subject analysis set title	Daptomycin 4 mg/kg: Ages 3 to 6 months - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	

Primary: Pharmacokinetics of daptomycin: Maximum plasma concentration

End point title	Pharmacokinetics of daptomycin: Maximum plasma concentration[1]
End point description:	
Maximum plasma concentration (Cmax) presented in micrograms per milliliter over the entire sampling phase directly obtained from the experimental plasma concentration time data, without interpolation.	
End point type	Primary
End point timeframe:	
Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start 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: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

End point values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	7	
Units: micrograms per millilitre				
arithmetic mean (standard deviation)	67 (± 14.5)	37.1 (± 12.6)	38.7 (± 5.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Area under the plasma concentration-time curve

End point title	Pharmacokinetics of daptomycin: Area under the plasma concentration-time curve[2]

End point description:

Area under the plasma concentration-time curve from 0 to infinity (AUC0-∞) presented in micrograms times hours per millilitre.

End point type	Primary

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion.

Notes:

[2] - 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: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

End point values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	7	
Units: micrograms times hours per millilitre				
arithmetic mean (standard deviation)	281.5 (± 44.5)	219.3 (± 66.8)	215 (± 68.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Time to maximum concentration

End point title	Pharmacokinetics of daptomycin: Time to maximum concentration[3]

End point description:

Time to maximum concentration (Tmax) in hours defined as the sampling time at which Cmax occurred, obtained directly from the experimental plasma concentration time data, without interpolation.

End point type	Primary

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start 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: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

End point values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	7	
Units: hours				
arithmetic mean (standard deviation)	0.66 (± 0.26)	0.59 (± 0.2)	0.53 (± 0.02)	

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Half-life

End point title	Pharmacokinetics of daptomycin: Half-life[4]

End point description:

The apparent elimination half-life (t1/2) of daptomycin presented in hours calculated as natural logarithm of 2 divided by the terminal slope of the concentration versus time curve (Kel).

End point type	Primary

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion.

Notes:

[4] - 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: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

End point values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	7	
Units: Hours				
arithmetic mean (standard deviation)	4.41 (± 0.94)	5.45 (± 1.13)	5.1 (± 1.17)	

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Clearance

End point title	Pharmacokinetics of daptomycin: Clearance[5]

End point description:

Plasma clearance (CL) calculated as dose divided by AUC0-∞ is presented in millilitres per hour(s) per kilogram.

End point type	Primary

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start 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: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

End point values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	7	
Units: millilitre(s) per hour(s) per kilogram				
arithmetic mean (standard deviation)	21.76 (± 2.99)	19.63 (± 5.76)	19.72 (± 5.46)	

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Volume of distribution

End point title	Pharmacokinetics of daptomycin: Volume of distribution[6]

End point description:

Steady state weight adjusted volume of distribution (Vss) presented in millilitres per kilogram calculated as a product of CL and mean residence time.

End point type	Primary

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion.

Notes:

[6] - 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: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

End point values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	7	
Units: Millilitre(s) per kilogram				
arithmetic mean (standard deviation)	121.7 (± 30.7)	134.9 (± 28.6)	127.7 (± 11.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety of daptomycin: Treatment-emergent related adverse events

End point title	Safety of daptomycin: Treatment-emergent related adverse events

End point description:

The number of subjects with at least one treatment-emergent related adverse event was reported by dosing group.

End point type	Secondary

End point timeframe:

Up to 9 days after dosing.

End point values	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	9	
Units: Subjects	0	3	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up through 9 days post-dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Daptomycin 6 mg/kg: Ages 13 months to 24 months
Reporting group description:	
Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.	
Reporting group title	Daptomycin 4 mg/kg: Ages 7 months to 12 months
Reporting group description:	
Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	
Reporting group title	Daptomycin 4 mg/kg: Ages 3 months to 6 months
Reporting group description:	
Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.	

Serious adverse events	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (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: 5 %

Non-serious adverse events	Daptomycin 6 mg/kg: Ages 13 months to 24 months	Daptomycin 4 mg/kg: Ages 7 months to 12 months	Daptomycin 4 mg/kg: Ages 3 months to 6 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	6 / 8 (75.00%)	3 / 9 (33.33%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)	3 / 8 (37.50%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Eosinophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Urine output decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Hyperreflexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypertonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Teething			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Skin exfoliation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2009	• Dosing for Group 1 (ages 13 months to 24 months) was changed from 9 mg/kg over a 1 hour infusion to 6 mg/kg over a 30 minute infusion. In addition, infusion times were updated for Group 2 (ages 7 months to 12 months)and Group 3 (ages 3 months to 6 months) to include the possibility of a 30 minute infusion. • Enrollment was to begin with Group 1. • Pharmacokinetic sampling time points were adjusted accordingly to account for the revised dosing.
02 September 2010	• Based on the review of clinical data from 4 infants in Age Group 1, the dose of study medication was reduced to 4 mg/kg administered over 30 minutes for children younger than 13 months of age (Age Groups 2 and 3). The 6 mg/kg dose, administered over 30 minutes, was continued for Age Group 1. Age Groups 2 and 3 were to be enrolled simultaneously. • An inclusion criterion was added that requires the presence of two patent i.v. lines (or comparable means of venous access) prior to dosing on Study Day 1. • The timing of PK plasma sample collection was revised to reflect the revised infusion schedule.
20 July 2011	• The option for a 1 hour or 2 hour infusion was removed since both dose groups received 4 mg/kg which was infused over 30 minutes. • The Baseline evaluation screening window was changed from 48 hour prior to dosing to 2 weeks prior to dosing to allow a larger window for screening. • To account for the difficulty placing 12 leads on the subjects in the youngest age group, the requirement for a 12-lead ECG was changed to an ECG. • Revision of inclusion criterion 5 to state that subjects had to have suspected or diagnosed bacterial infection instead of a gram positive infection. The subject was also to have received standard antibiotic therapy, including prophylactic use of antibiotics peri-operatively. • Revisions of various other inclusion and exclusion criteria. • Concomitant antibiotics and medications and concurrent procedures was revised to account for the inclusion of surgical subjects. The following changes were made: the requirements that surgical procedures could not be performed within 24 hours prior to dosing and that subjects were not to plan procedures in the 24 hours following dosing were deleted. • The number of samples required for PK collection was reduced from 6 to 5, thus eliminating the pre-dose draw.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported