



Clinical trial results:

An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged Two to Six Years Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection

Summary

EudraCT number	2015-002781-23
Trial protocol	Outside EU/EEA
Global end of trial date	20 November 2008

Results information

Result version number	v1 (current)
This version publication date	05 April 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	DAP-PEDS-07-02
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00679835
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cubist Pharmaceuticals
Sponsor organisation address	65 Hayden Avenue, Lexington, United States, 02421
Public contact	Medical Director, Cubist Pharmaceuticals, +1 781-860-8660 ,
Scientific contact	Medical 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	26 May 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2008
Global end of trial reached?	Yes
Global end of trial date	20 November 2008
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 pharmacokinetic (PK) data on intravenous (i.v.) daptomycin administered at 8 milligrams per kilogram (mg/kg) as a 1 hour infusion or 10 mg/kg as either a 1 or 2 hour infusion in pediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infection who were receiving standard antibiotic therapy.

Protection of trial subjects:

This open-label study did not employ any blinding methods. Screening assessments included demographics and medical history, physical examination, vital signs, brief neurologic examination, electrocardiogram, and clinical laboratory tests (chemistry, hematology, urinalysis, serum creatinine, and serum creatine phosphokinase). Study subjects were monitored for adverse events. After the first 6 subjects enrolled in Group 1 had completed laboratory testing and the follow-up visit, the Investigators and the Sponsor's medical and PK representatives reviewed pertinent PK and safety data and decided whether or not to continue enrollment to 12 subjects.

Background therapy: -

Evidence for comparator:

This was a non-comparative study.

Actual start date of recruitment	03 June 2008
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: 12
Worldwide total number of subjects	12
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)	0
Children (2-11 years)	12

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 and written subject assent (as appropriate) was obtained, 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 8 mg/kg

Arm description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

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 8 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 1 hour via a syringe pump. The dosing volume was 25 millilitres (mL) and the infusion rate was 0.42 mL per minute for the 1-hour infusion.

Arm title	Daptomycin 10 mg/kg
------------------	---------------------

Arm description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

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 10 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 1 hour via a syringe pump. The dosing volume was 25 mL and the infusion rate was 0.42 mL per minute for the 1-hour infusion.

Number of subjects in period 1	Daptomycin 8 mg/kg	Daptomycin 10 mg/kg
Started	6	6
Subjects that received a complete dose	6	6
Completed	6	6

Baseline characteristics

Reporting groups

Reporting group title	Daptomycin 8 mg/kg
-----------------------	--------------------

Reporting group description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

Reporting group title	Daptomycin 10 mg/kg
-----------------------	---------------------

Reporting group description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

Reporting group values	Daptomycin 8 mg/kg	Daptomycin 10 mg/kg	Total
Number of subjects	6	6	12
Age categorical			
Age of all enrolled subjects by category.			
Units: Subjects			
Children (2-11 years)	6	6	12
Age continuous			
Age of all enrolled subjects.			
Units: years			
arithmetic mean	3.85	4.43	
standard deviation	± 1.88	± 1.136	-
Gender categorical			
Gender of all enrolled subjects.			
Units: Subjects			
Female	3	2	5
Male	3	4	7

End points

End points reporting groups

Reporting group title	Daptomycin 8 mg/kg
Reporting group description: Subjects received a single dose of daptomycin over a duration of 1 hour.	
Reporting group title	Daptomycin 10 mg/kg
Reporting group description: Subjects received a single dose of daptomycin over a duration of 1 hour.	

Primary: Pharmacokinetics of daptomycin: Apparent elimination half-life

End point title	Pharmacokinetics of daptomycin: Apparent elimination half-
End point description: The apparent elimination half-life ($t_{1/2}$) of daptomycin presented in hours calculated as natural logarithm of 2 divided by the terminal slope of the concentration versus time curve (K_{el}).	
End point type	Primary
End point timeframe: Up to 24 hours post dose.	
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 8 mg/kg	Daptomycin 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hours				
arithmetic mean (standard deviation)	5.35 (\pm 1.41)	5.67 (\pm 0.62)		

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 ^[2]
End point description: Terminal exponential volume of distribution (V_z) presented in millilitres per kilogram based on the terminal phase calculated as the ratio of plasma clearance (CL) and K_{el} .	
End point type	Primary
End point timeframe: Up to 24 hours post dose.	
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 8 mg/kg	Daptomycin 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: millilitre(s) per kilogram				
arithmetic mean (standard deviation)	142.3 (\pm 12.28)	154.8 (\pm 32.98)		

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Maximum plasma concentration

End point title	Pharmacokinetics of daptomycin: Maximum plasma concentration ^[3]
-----------------	---

End point description:

Maximum plasma concentration (C_{max}) presented in micrograms per millilitre over the entire sampling phase directly obtained from the experimental plasma concentration time data, without interpolation.

End point type	Primary
----------------	---------

End point timeframe:

Up to 24 hours post dose.

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 8 mg/kg	Daptomycin 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: microgram(s) per millilitre				
arithmetic mean (standard deviation)	68.42 (\pm 9.33)	79.18 (\pm 10.17)		

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 ^[4]
-----------------	--

End point description:

Time to maximum concentration (T_{max}) presented in hours defined as the sampling time at which C_{max} occurred, obtained directly from the experimental plasma concentration time data, without interpolation.

End point type	Primary
----------------	---------

End point timeframe:

Up to 24 hours post dose.

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 8 mg/kg	Daptomycin 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: hours				
arithmetic mean (standard deviation)	0.86 (± 0.27)	1.04 (± 0.04)		

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 ^[5]
-----------------	---

End point description:

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

End point type	Primary
----------------	---------

End point timeframe:

Up to 24 hours post dose.

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 8 mg/kg	Daptomycin 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: microgram(s) times hours per millilitre				
arithmetic mean (standard deviation)	429.14 (± 113.01)	549.7 (± 139.35)		

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Clearance

End point title	Pharmacokinetics of daptomycin: Clearance ^[6]
-----------------	--

End point description:

Plasma clearance (CL) calculated as dose divided by AUC_{0-∞} is presented in millilitres per hour(s) per kilogram.

End point type	Primary
----------------	---------

End point timeframe:

Up to 24 hours post dose.

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 8 mg/kg	Daptomycin 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: millilitre(s) per hour(s) per kilogram				
arithmetic mean (standard deviation)	19.47 (± 5.01)	19.14 (± 4.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety of daptomycin: Treatment-emergent adverse events

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

End point description:

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

End point type	Secondary
----------------	-----------

End point timeframe:

Up to 9 days after dosing.

End point values	Daptomycin 8 mg/kg	Daptomycin 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	6		
Units: Subjects	2	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up through 7 days post-dose.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	11.0
--------------------	------

Reporting groups

Reporting group title	Daptomycin 10 mg/kg
-----------------------	---------------------

Reporting group description: -

Reporting group title	Daptomycin 8 mg/kg
-----------------------	--------------------

Reporting group description: -

Serious adverse events	Daptomycin 10 mg/kg	Daptomycin 8 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
GROIN ABSCESS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (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	Daptomycin 10 mg/kg	Daptomycin 8 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	
Investigations			
BODY TEMPERATURE INCREASED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
PHLEBITIS			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
HYPOAESTHESIA subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
General disorders and administration site conditions CATHETER RELATED COMPLICATION subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
IRRITABILITY subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	
Ear and labyrinth disorders CERUMEN IMPACTION subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
TONSILLAR HYPERTROPHY subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	
Skin and subcutaneous tissue disorders DRY SKIN subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
PRURITUS subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	
Musculoskeletal and connective tissue disorders			

PAIN IN EXTREMITY			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

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

None reported