Clinical trial results:
An Evaluation of the Safety, Efficacy and Pharmacokinetics of Daptomycin in Pediatric Subjects Aged One to Seventeen Years With Complicated Skin and Skin Structure Infections Caused by Gram-Positive Pathogens

Summary

EudraCT number	2015-002778-19
Trial protocol	Outside EU/EEA
Global end of trial date	01 October 2013

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-07-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00711802
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cubist Pharmaceuticals, Inc.
Sponsor organisation address	65 Hayden Avenue, Lexington,, United States, 02421
Public contact	Medical Director, Cubist Pharmaceuticals, Inc., 001 781860-8660,
Scientific contact	Medical Director, Cubist Pharmaceuticals, Inc., 001 781860-8660,

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	02 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2013
Global end of trial reached?	Yes
Global end of trial date	01 October 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of age dependent doses of intravenous (IV) daptomycin administered for up to 14 days in comparison with standard of care (SOC) therapy in pediatric subjects aged 1 to 17 years with complicated skin and skin structure infections (cSSSI) caused by Gram-positive pathogens.

Protection of trial subjects:

This study was conducted in compliance with institutional review board (IRB)/independent ethics committee (IEC) and International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline, and any local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2008
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	India: 123
Country: Number of subjects enrolled	United States: 273
Worldwide total number of subjects	396
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)	45
Children (2-11 years)	234
Adolescents (12-17 years)	117
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:

Subjects in this study were between the ages of 1 to 17 years, inclusive, with complicated skin and skin structure infection (cSSSI) caused by Gram-positive pathogens. Subjects were eligible to participate in the study if they met all of the inclusion criteria and none of the exclusion criteria at the screening visit.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

This was an evaluator-blinded study. The maintenance of the study blind was critical for an unbiased review of the safety and efficacy of the study drug. Therefore a site blinding plan was developed at each site detailing exactly how the blind was maintained throughout the study. Prior to study start at each site, a physician was designated the blinded Investigator. The unblinded evaluator was responsible for all other study-related procedures and assessments and followed the subject daily.

Arms

Are arms mutually exclusive?	Yes
Arm title	Daptomycin

Arm description:

Administered intravenously (IV) every 24 hours for up to 14 days at age-dependent dosages.

Arm type	Experimental
Investigational medicinal product name	Daptomycin
Investigational medicinal product code	
Other name	Cubicin
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously (IV) every 24 hours for up to 14 days at the following age-dependent dosages.
Subjects ages 7 to 17 years: daptomycin was dissolved in a volume of 50 millilitres (mL) 0.9% sodium chloride for injection over 30 minutes (min) with an infusion rate of 1.67 mL/min.
Subjects 1 to 6 years-old: daptomycin was dissolved in a volume of 25 mL 0.9% sodium chloride for injection over 60 min with an infusion rate was 0.42 mL/min.
Age Group 1 (for ages 12 to 17 years): 5 milligrams/kilogram (mg/kg)
Age Group 2 (for ages 7 to 11 years): 7 mg/kg
Age Group 3 (for ages 2 to 6 years): 9 mg/kg
Age Group 4 (for ages 1 to <2 years): 10 mg/kg

Arm title	Standard of Care (SOC)

Arm description:

The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator.

Arm type	Active comparator

Investigational medicinal product name	Standard of Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This was an evaluator-blinded study. The maintenance of the study blind was critical for an unbiased review of the safety and efficacy of the study drug. Therefore a site blinding plan was developed at each site detailing exactly how the blind was maintained throughout the study. Prior to study start at each site, a physician was designated the blinded Investigator. The unblinded evaluator was responsible for all other study-related procedures and assessments and followed the subject daily.

Number of subjects in period 1	Daptomycin	Standard of Care (SOC)
Started	263	133
Received at least 1 dose of study drug	257	132
Completed	236	114
Not completed	27	19
Physician decision	-	2
Consent withdrawn by subject	-	2
Microbiological failure	-	2
Reason not reported (no further details)	3	1
Adverse event, non-fatal	1	1
Not treated (no further details)	6	1
Lost to follow-up	17	9
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study (overall period)

Reporting group description: -

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	396	396	
Age categorical Units: Subjects			

Age continuous			
For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available.			
Units: years arithmetic mean standard deviation	 8.21 ± 5.134	 -	
Gender categorical			
Gender was not known for 7 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	188	188	
Male	208	208	

Subject analysis sets

Subject analysis set title	Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received at least 1 dose of study drug.

Subject analysis set title	Standard of Care (SOC)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received at least 1 dose of study drug.

Subject analysis set title	Age Group 1: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 5 mg/kg administered IV every 24 hours for up to 14 days
Age Group 1: Participants ages 12 to 17 years

Subject analysis set title	Age Group 1: Standard of Care (SOC)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 1: Participants ages 12 to 17 years

Subject analysis set title	Age Group 2: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 7 mg/kg administered IV every 24 hours for up to 14 days
Age Group 2: Participants ages 7 to 11 years

Subject analysis set title	Age Group 2: SOC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 2: Participants ages 7 to 11 years

Subject analysis set title	Age Group 3: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 9 mg/kg administered IV every 24 hours for up to 14 days
Age Group 3: Participants ages 2 to 6 years

Subject analysis set title	Age Group 3: SOC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 3: Participants ages 2 to 6 years

Subject analysis set title	Age Group 4: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 10 mg/kg administered IV every 24 hours for up to 14 days
Age Group 4: Participants ages 1 to <2 years

Subject analysis set title	Age Group 4: SOC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 4: Participants ages 1 to <2 years

Reporting group values	Daptomycin	Standard of Care (SOC)	Age Group 1: Daptomycin
Number of subjects	257	132	73
Age categorical Units: Subjects			
Age continuous			
For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available.			
Units: years arithmetic mean standard deviation	 8.25 ± 5.162	 8.14 ± 5.098	 15.02 ± 1.584
Gender categorical			
Gender was not known for 7 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	126	62	29

Male	131	70	44

Reporting group values	Age Group 1: Standard of Care (SOC)	Age Group 2: Daptomycin	Age Group 2: SOC
Number of subjects	37	73	38
Age categorical			
Units: Subjects			

Age continuous			
For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available.			
Units: years			
arithmetic mean	14.84	9.05	8.98
standard deviation	± 1.735	± 1.443	± 1.305
Gender categorical			
Gender was not known for 7 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	28	15
Male	22	45	23

Reporting group values	Age Group 3: Daptomycin	Age Group 3: SOC	Age Group 4: Daptomycin
Number of subjects	81	42	30
Age categorical			
Units: Subjects			

Age continuous			
For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available.			
Units: years			
arithmetic mean	3.92	3.86	1.46
standard deviation	± 1.556	± 1.555	± 0.231
Gender categorical			
Gender was not known for 7 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	48	20	21
Male	33	22	9

Reporting group values	Age Group 4: SOC		
Number of subjects	15		
Age categorical			
Units: Subjects			

Age continuous			
For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available.			
Units: years			
arithmetic mean	1.43		
standard deviation	± 0.299		

Gender categorical			
Gender was not known for 7 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	12		
Male	3		

End points

End points reporting groups

Reporting group title	Daptomycin

Reporting group description:

Administered intravenously (IV) every 24 hours for up to 14 days at age-dependent dosages.

Reporting group title	Standard of Care (SOC)

Reporting group description:

The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator.

Subject analysis set title	Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received at least 1 dose of study drug.

Subject analysis set title	Standard of Care (SOC)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who received at least 1 dose of study drug.

Subject analysis set title	Age Group 1: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 5 mg/kg administered IV every 24 hours for up to 14 days
Age Group 1: Participants ages 12 to 17 years

Subject analysis set title	Age Group 1: Standard of Care (SOC)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 1: Participants ages 12 to 17 years

Subject analysis set title	Age Group 2: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 7 mg/kg administered IV every 24 hours for up to 14 days
Age Group 2: Participants ages 7 to 11 years

Subject analysis set title	Age Group 2: SOC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 2: Participants ages 7 to 11 years

Subject analysis set title	Age Group 3: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 9 mg/kg administered IV every 24 hours for up to 14 days
Age Group 3: Participants ages 2 to 6 years

Subject analysis set title	Age Group 3: SOC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 3: Participants ages 2 to 6 years

Subject analysis set title	Age Group 4: Daptomycin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Daptomycin: 10 mg/kg administered IV every 24 hours for up to 14 days
Age Group 4: Participants ages 1 to <2 years

Subject analysis set title	Age Group 4: SOC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 4: Participants ages 1 to <2 years

Primary: Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

A TEAE was defined as any treatment-emergent adverse event (AE) that occurred from the time of first dose of the study drug through the last study evaluation or pre-existing adverse AEs that were aggravated in severity or frequency during the dosing period. The percentage of participants with at least 1 TEAE is presented.

End point type	Primary

End point timeframe:

Baseline (Day 1) through 14 days after last dose of study drug

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not planned or performed for this endpoint.

End point values	Daptomycin	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256[2]	133[3]		
Units: percentage				
number (not applicable)	38.3	36.1		

Notes:

[2] - Participants who received at least 1 dose of study drug with evaluable post-baseline TEAE data.

[3] - Participants who received at least 1 dose of study drug with evaluable post-baseline TEAE data.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an Overall Therapeutic Response at Test of Cure Visit

End point title	Percentage of Participants With an Overall Therapeutic Response at Test of Cure Visit

End point description:

The assessment of therapeutic response was determined by comparing a participant's signs and

symptoms at the test of cure visit (up to 14 days after last dose) to those recorded at baseline. Participants were classified as "Success" or "Failure" by combining their clinical and microbiological efficacy responses. Resolution of clinically significant signs and symptoms associated with the skin infection present at study baseline was considered "Success" by the Investigator. These participants were deemed both clinically cured and microbiologically eradicated. For participants whose clinical course could not be clearly defined as improved, a clinical outcome of "Failure" was rendered. In addition, if it was determined that the primary site of infection required additional antibiotic treatment, the assessment of clinical response was "Failure." If the Investigator was unable to determine a response because the participant was lost to follow-up, the assessment was "Unable to evaluate."

End point type	Secondary

End point timeframe:

Test of cure visit--14 days after last dose of study drug

End point values	Daptomycin	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[4]	105[5]		
Units: Percentage				
number (not applicable)				
Clinical success	88.6	87.6		
Clinical failure	1	1		
Unable to evaluate	10.5	11.4		

Notes:

[4] - Participants who received at least 1 dose of study drug with evaluable test-of-cure visit data.

[5] - Participants who received at least 1 dose of study drug with evaluable test-of-cure visit data.

Statistical analyses

Statistical analysis title	Percent difference in success rate

Statistical analysis description:

Success rate was calculated as the number of subjects with clinical success at each visit divided by the total number of subjects with outcome at that visit. The difference in success rate was calculated as success rate for daptomycin minus rate for standard of care.

Comparison groups	Daptomycin v Standard of Care (SOC)
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Percent difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.75
upper limit	8.5

Notes:

[6] - The study was not powered for the test of non-inferiority for the primary or the secondary endpoints; however, in Age Groups 1, 2, and 3 with observed success rates of 80% and the minimum of 50 daptomycin and 25 SOC subjects in each age group, the distance from the difference in rates to each 95% confidence bound, is 0.22.

Secondary: Pharmacokinetics (PK): Area Under the Plasma Concentration-Time Curve for Daptomycin From 0 to the Last Sampling Time Point (AUC[0-t])

End point title	Pharmacokinetics (PK): Area Under the Plasma Concentration-Time Curve for Daptomycin From 0 to the Last Sampling Time

	Point (AUC[0-t])

End point description:

Participants who volunteered for PK sampling had a blood sample collected for analysis at the following time points:
Age Group 1; Day 3: Predose, 0.25 hour (hr), 1 hr, 4 hr, and12 hr postdose. Age Group 2; Day 3: Predose, 0.25 hr, 1 hr, 6 hr, and 10 hr postdose. Age Group 3; Day 1, 2, or 3: Predose, 0.25 hr, 1 hr, 6 hr, and 8 hr postdose. Age Group 4; Day 1, 2, or 3: 0, 1, 2, 4, and 6 hr relative to end of infusion.

Due to limited PK samples, where measures could not be calculated, a "0" is reported.
Due to limited PK samples, PK parameters were computed using the mean concentration-time profile during a sampling interval. As a result, no variability could be calculated for data where "0" is reported.

End point type	Secondary

End point timeframe:

Predose and 5 timepoints according to age group (up to 12 hours postdose).

End point values	Age Group 1: Daptomycin	Age Group 2: Daptomycin	Age Group 3: Daptomycin	Age Group 4: Daptomycin
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[7]	2[8]	7[9]	30[10]
Units: microgram*hour per milliliter (µg*hr/mL)				
arithmetic mean (standard deviation)	318 (± 62.2)	0 (± 0)	318 (± 68.6)	466 (± 0)

Notes:

[7] - Participants who received at least 1 dose of study drug with evaluable daptomycin AUC(0-t) data.

[8] - Participants who received at least 1 dose of study drug with evaluable daptomycin AUC(0-t) data.

[9] - Participants who received at least 1 dose of study drug with evaluable daptomycin AUC(0-t) data.

[10] - Participants who received at least 1 dose of study drug with evaluable daptomycin AUC(0-t) data.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for adverse events from Screening (within 48 hours of 1st dose of study drug) through the last study evaluation visit (7-14 days after the last dose of study drug).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Age Group 4: Daptomycin

Reporting group description:

Daptomycin: 10 mg/kg administered IV every 24 hours for up to 14 days
Age Group 4: Participants ages 1 to <2 years

Reporting group title	Age Group 1: Daptomycin

Reporting group description:

Daptomycin: 5 mg/kg administered IV every 24 hours for up to 14 days
Age Group 1: Participants ages 12 to 17 years

Reporting group title	Age Group 2: Daptomycin

Reporting group description:

Daptomycin: 7 mg/kg administered IV every 24 hours for up to 14 days
Age Group 2: Participants ages 7 to 11 years

Reporting group title	Age Group 3: Daptomycin

Reporting group description:

Daptomycin: 9 mg/kg administered IV every 24 hours for up to 14 days
Age Group 3: Participants ages 2 to 6 years

Reporting group title	Standard of Care

Reporting group description:

SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.
Age Group 4: Participants ages 1 to <2 years

Serious adverse events	Age Group 4: Daptomycin	Age Group 1: Daptomycin	Age Group 2: Daptomycin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	3 / 72 (4.17%)	1 / 73 (1.37%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Wound drainage			
subjects affected / exposed	0 / 30 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 72 (1.39%)	0 / 73 (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
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Status asthmaticus			
subjects affected / exposed	0 / 30 (0.00%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 72 (1.39%)	0 / 73 (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
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 30 (0.00%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 30 (0.00%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 30 (0.00%)	1 / 72 (1.39%)	0 / 73 (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
Toxic shock syndrome			
subjects affected / exposed	0 / 30 (0.00%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Age Group 3: Daptomycin	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 81 (2.47%)	3 / 133 (2.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 81 (0.00%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Wound drainage			
subjects affected / exposed	0 / 81 (0.00%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 81 (0.00%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 81 (1.23%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Status asthmaticus			
subjects affected / exposed	1 / 81 (1.23%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	0 / 81 (0.00%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 81 (0.00%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 81 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 81 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 81 (0.00%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic shock syndrome			

subjects affected / exposed	0 / 81 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Age Group 4: Daptomycin	Age Group 1: Daptomycin	Age Group 2: Daptomycin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 30 (33.33%)	13 / 72 (18.06%)	6 / 73 (8.22%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 30 (3.33%)	4 / 72 (5.56%)	0 / 73 (0.00%)
occurrences (all)	1	4	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 30 (0.00%)	5 / 72 (6.94%)	2 / 73 (2.74%)
occurrences (all)	0	5	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 72 (2.78%)	4 / 73 (5.48%)
occurrences (all)	2	2	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)	3 / 72 (4.17%)	3 / 73 (4.11%)
occurrences (all)	0	3	3
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	0 / 72 (0.00%)	1 / 73 (1.37%)
occurrences (all)	3	0	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 30 (6.67%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Dermatitis diaper			

subjects affected / exposed	2 / 30 (6.67%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Rash papular			
subjects affected / exposed	2 / 30 (6.67%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences (all)	2	1	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 30 (6.67%)	1 / 72 (1.39%)	0 / 73 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 72 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Age Group 3: Daptomycin	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 81 (30.86%)	20 / 133 (15.04%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	8 / 81 (9.88%)	7 / 133 (5.26%)	
occurrences (all)	8	7	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 81 (0.00%)	3 / 133 (2.26%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 81 (1.23%)	4 / 133 (3.01%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 81 (14.81%)	7 / 133 (5.26%)	
occurrences (all)	13	7	
Vomiting			
subjects affected / exposed	4 / 81 (4.94%)	1 / 133 (0.75%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal			

disorders Rhinorrhoea subjects affected / exposed occurrences (all)	 2 / 81 (2.47%) 2	 1 / 133 (0.75%) 1	
Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all) Rash papular subjects affected / exposed occurrences (all)	 0 / 81 (0.00%) 0 0 / 81 (0.00%) 0	 3 / 133 (2.26%) 3 1 / 133 (0.75%) 1	
Infections and infestations Cellulitis subjects affected / exposed occurrences (all)	 1 / 81 (1.23%) 1	 0 / 133 (0.00%) 0	
Metabolism and nutrition disorders Hyperphosphataemia subjects affected / exposed occurrences (all)	 1 / 81 (1.23%) 1	 0 / 133 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported