



Clinical trial results:

A Comparative Evaluation of the Safety and Efficacy of Daptomycin Versus Standard of Care in Pediatric Subjects One - Seventeen Years of Age with Bacteremia Caused by Staphylococcus Aureus

Summary

EudraCT number	2012-003447-29
Trial protocol	IT ES HU GR Outside EU/EEA
Global end of trial date	20 January 2016

Results information

Result version number	v2 (current)
This version publication date	05 August 2016
First version publication date	29 June 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	3009-005
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01728376
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cubist Pharmaceuticals LLC
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

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	20 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2016
Global end of trial reached?	Yes
Global end of trial date	20 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the safety of intravenous (i.v.) daptomycin versus standard of care antibiotics in pediatric participants aged 1-17 years with *S. aureus* bacteremia.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

The following additional measures defined for this individual study were in place for the protection of trial participants: A stepwise approach was implemented to gate enrollment as follows: enrollment began with children aged 4-17 years; after an external Data Monitoring Committee (DMC) review, enrollment was broadened to 1-17 years. A longer daptomycin infusion time (60 minutes) was proposed for children below the age of 6 years to blunt the maximum serum concentration (C_{max}), a parameter associated with potential adverse nerve effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2012
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	Argentina: 3
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Panama: 7
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Ukraine: 25
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	82
EEA total number of subjects	2

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)	61
Adolescents (12-17 years)	21
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants aged 1-17 with bacteremia caused by *S. aureus* were enrolled in this study. Additional inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

Participants were screened and their eligibility determined within 72 hours prior to study medication administration.

Period 1

Period 1 title	Intravenous (i.v.) Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Daptomycin (1-6 year olds)

Arm description:

Participants aged 1-6 years were administered daptomycin 12 mg/kg, infused once daily, intravenously, over 60 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.

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

Dosage and administration details:

12 mg/kg once daily infused over 60 ± 6 minutes

Arm title	Comparator (1-6 year olds)
------------------	----------------------------

Arm description:

Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.

Arm type	Active comparator
Investigational medicinal product name	vancomycin (i.v.), clindamycin (i.v.), semi-synthetic penicillins (i.v.) (nafcillin, oxacillin, or cloxacillin), or first-generation cephalosporins (i.v.)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per standard of care

Arm title	Daptomycin (7-11 year olds)
------------------	-----------------------------

Arm description:

Participants aged 7-11 years were administered daptomycin 9 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Daptomycin
Investigational medicinal product code	
Other name	Cubicin®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
9 mg/kg once daily infused over 30 ± 3 minutes	
Arm title	Comparator (7-11 year olds)

Arm description:

Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.

Arm type	Active comparator
Investigational medicinal product name	vancomycin (i.v.), clindamycin (i.v.), semi-synthetic penicillins (i.v.) (nafcillin, oxacillin, or cloxacillin), or first-generation cephalosporins (i.v.)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per standard of care

Arm title	Daptomycin (12-17 year olds)
------------------	------------------------------

Arm description:

Participants aged 12-17 were administered daptomycin 7 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days.

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

Dosage and administration details:

7 mg/kg once daily infused over 30 ± 3 minutes

Arm title	Comparator (12-17 year olds)
------------------	------------------------------

Arm description:

Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days.

Arm type	Active comparator
Investigational medicinal product name	vancomycin (i.v.), clindamycin (i.v.), semi-synthetic penicillins (i.v.) (nafcillin, oxacillin, or cloxacillin), or first-generation cephalosporins (i.v.)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered per standard of care

Number of subjects in period 1	Daptomycin (1-6 year olds)	Comparator (1-6 year olds)	Daptomycin (7-11 year olds)
Started	22	11	19
Treated	22	10	19
Completed	18	10	17
Not completed	4	1	2
Persistent Positive Blood Cultures	1	-	1
Adverse event, non-fatal	1	-	1
No relevant bacteria, participant discharged, etc.	2	-	-
Subject/Parent/Legal Guardian Decision	-	-	-
Did not receive treatment	-	1	-

Number of subjects in period 1	Comparator (7-11 year olds)	Daptomycin (12-17 year olds)	Comparator (12-17 year olds)
Started	9	14	7
Treated	9	14	7
Completed	8	12	5
Not completed	1	2	2
Persistent Positive Blood Cultures	-	-	-
Adverse event, non-fatal	-	1	-
No relevant bacteria, participant discharged, etc.	-	1	1
Subject/Parent/Legal Guardian Decision	1	-	1
Did not receive treatment	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	Daptomycin (1-6 year olds)
Reporting group description: Participants aged 1-6 years were administered daptomycin 12 mg/kg, infused once daily, intravenously, over 60 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Comparator (1-6 year olds)
Reporting group description: Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Daptomycin (7-11 year olds)
Reporting group description: Participants aged 7-11 years were administered daptomycin 9 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Comparator (7-11 year olds)
Reporting group description: Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Daptomycin (12-17 year olds)
Reporting group description: Participants aged 12-17 were administered daptomycin 7 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days.	
Reporting group title	Comparator (12-17 year olds)
Reporting group description: Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days.	

Reporting group values	Daptomycin (1-6 year olds)	Comparator (1-6 year olds)	Daptomycin (7-11 year olds)
Number of subjects	22	11	19
Age Categorical Units: Subjects			
Children (2-11 years)	22	11	19
Adolescents (12-17 years)	0	0	0
Age Continuous Units: years			
arithmetic mean	3.8	4.1	10.3
standard deviation	± 1.2	± 1.7	± 1.2
Gender Categorical Units: Subjects			
Female	10	9	7
Male	12	2	12

Reporting group values	Comparator (7-11 year olds)	Daptomycin (12-17 year olds)	Comparator (12-17 year olds)
Number of subjects	9	14	7

Age Categorical			
Units: Subjects			
Children (2-11 years)	9	0	0
Adolescents (12-17 years)	0	14	7
Age Continuous			
Units: years			
arithmetic mean	9.5	14.1	14.6
standard deviation	± 1.3	± 1.7	± 1.9
Gender Categorical			
Units: Subjects			
Female	1	0	1
Male	8	14	6

Reporting group values	Total		
Number of subjects	82		
Age Categorical			
Units: Subjects			
Children (2-11 years)	61		
Adolescents (12-17 years)	21		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Units: Subjects			
Female	28		
Male	54		

End points

End points reporting groups

Reporting group title	Daptomycin (1-6 year olds)
Reporting group description: Participants aged 1-6 years were administered daptomycin 12 mg/kg, infused once daily, intravenously, over 60 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Comparator (1-6 year olds)
Reporting group description: Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Daptomycin (7-11 year olds)
Reporting group description: Participants aged 7-11 years were administered daptomycin 9 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Comparator (7-11 year olds)
Reporting group description: Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days.	
Reporting group title	Daptomycin (12-17 year olds)
Reporting group description: Participants aged 12-17 were administered daptomycin 7 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days.	
Reporting group title	Comparator (12-17 year olds)
Reporting group description: Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days.	
Subject analysis set title	Daptomycin (1-6 years) - mMITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants aged 1-6 years were administered daptomycin 12 mg/kg, infused once daily, intravenously, over 60 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The Microbiological Modified Intent-to-Treat (mMITT) population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven <i>S. aureus</i> bacteremia at baseline.	
Subject analysis set title	Daptomycin (7-11 years) - mMITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants aged 7-11 years were administered daptomycin 9 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The mMITT population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven <i>S. aureus</i> bacteremia at baseline.	
Subject analysis set title	Daptomycin (12-17 years) - mMITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants aged 12-17 were administered daptomycin 7 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days. The mMITT population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven <i>S. aureus</i> bacteremia at baseline.	
Subject analysis set title	Comparator (1-6 years) - mMITT

Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The mMITT population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven <i>S. aureus</i> bacteremia at baseline.	
Subject analysis set title	Comparator (7-11 years) - mMITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The mMITT population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven <i>S. aureus</i> bacteremia at baseline.	
Subject analysis set title	Comparator (12-17 years) - mMITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days. The mMITT population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven <i>S. aureus</i> bacteremia at baseline.	
Subject analysis set title	Daptomycin (1-6 years) - ER
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged 1-6 years were administered daptomycin 12 mg/kg, infused once daily, intravenously, over 60 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The Exposure Response (ER) population consists of any participant with at least one peak or trough plasma sample.	
Subject analysis set title	Daptomycin (7-11 years) - ER
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged 7-11 years were administered daptomycin 9 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The ER population consists of any participant with at least one peak or trough plasma sample.	
Subject analysis set title	Daptomycin (12-17 years) - ER
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants aged 12-17 were administered daptomycin 7 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days. The ER population consists of any participant with at least one peak or trough plasma sample.	
Subject analysis set title	Daptomycin (1-6 years) - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants aged 1-6 years were administered daptomycin 12 mg/kg, infused once daily, intravenously, over 60 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The Safety population includes all participants who receive any dose of i.v. study medication (daptomycin or standard of care [SOC]); participants are categorized by actual treatment received, irrespective of the randomization assignment.	
Subject analysis set title	Daptomycin (7-11 years) - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants aged 7-11 years were administered daptomycin 9 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The Safety population includes all participants who receive any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.	

Subject analysis set title	Daptomycin (12-17 years) - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants aged 12-17 were administered daptomycin 7 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days. The Safety population includes all participants who receive any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.	
Subject analysis set title	Comparator (1-6 years) - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The Safety population includes all participants who receive any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.	
Subject analysis set title	Comparator (7-11 years) - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. The Safety population includes all participants who receive any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.	
Subject analysis set title	Comparator (12-17 years) - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days. The Safety population includes all participants who receive any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.	

Primary: Number of Participants with One or More Treatment-Emergent Adverse Events (AEs) During I.V. Treatment Phase

End point title	Number of Participants with One or More Treatment-Emergent Adverse Events (AEs) During I.V. Treatment Phase ^[1]
End point description:	
An AE is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The Safety population includes all participants who received any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment. AEs were collected from first dose of study medication through last follow-up visit for all randomized and treated participants.	
End point type	Primary
End point timeframe:	
Administration of first dose through the last follow-up visit (up to 77 days)	

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: Since the study was not powered for making inferential statistical analyses for safety, only descriptive statistics were provided for the endpoint.

End point values	Daptomycin (1-6 years) - Safety	Daptomycin (7-11 years) - Safety	Daptomycin (12-17 years) - Safety	Comparator (1-6 years) - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	19	14	10
Units: Participants	12	11	6	5

End point values	Comparator (7-11 years) - Safety	Comparator (12-17 years) - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	7		
Units: Participants	8	5		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with One or More Treatment-Emergent Serious Adverse Events (SAEs) During I.V. Treatment Phase

End point title	Number of Participants with One or More Treatment-Emergent Serious Adverse Events (SAEs) During I.V. Treatment Phase ^[2]
-----------------	-------------------------------------------------------------------------------------------------------------------------------------

End point description:

An SAE is any adverse experience occurring at any dose that results in any of the following outcomes: death, life-threatening experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is considered to be an important medical event. The Safety population includes all participants who received any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment. SAEs were collected from first dose of study medication through last follow-up visit for all randomized and treated participants.

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

End point timeframe:

Administration of first dose through the last follow-up visit (up to 77 days)

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: Since the study was not powered for making inferential statistical analyses for safety, only descriptive statistics were provided for the endpoint.

End point values	Daptomycin (1-6 years) - Safety	Daptomycin (7-11 years) - Safety	Daptomycin (12-17 years) - Safety	Comparator (1-6 years) - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	19	14	10
Units: Participants	2	2	1	0

End point values	Comparator (7-11 years) - Safety	Comparator (12-17 years) - Safety		
------------------	----------------------------------	-----------------------------------	--	--

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	7		
Units: Participants	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Maximum Post-Baseline Creatine Phosphokinase (CPK) Elevations Above Upper Limit of Normal

End point title	Percentage of Participants with Maximum Post-Baseline Creatine Phosphokinase (CPK) Elevations Above Upper Limit of Normal ^[3]
-----------------	------------------------------------------------------------------------------------------------------------------------------------------

End point description:

The percentage of participants with maximum post-baseline CPK elevations >500 Units Per Liter (U/L) is presented. The Safety population includes all participants who received any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.

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

End point timeframe:

Baseline up to end of therapy visit (up to 44 days)

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: Since the study was not powered for efficacy, inferential statistical analyses were neither planned nor performed for this endpoint.

End point values	Daptomycin (1-6 years) - Safety	Daptomycin (7-11 years) - Safety	Daptomycin (12-17 years) - Safety	Comparator (1-6 years) - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	19	14	10
Units: Percentage of Participants				
number (not applicable)	40.9	10.5	28.6	40

End point values	Comparator (7-11 years) - Safety	Comparator (12-17 years) - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	7		
Units: Percentage of Participants				
number (not applicable)	0	14.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Sustained CPK Elevations

End point title	Percentage of Participants with Sustained CPK Elevations ^[4]
End point description: The percentage of participants with sustained CPK elevations, defined as two consecutive post-baseline values above the ULN, is presented. The Safety population includes all participants who received any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.	
End point type	Primary
End point timeframe: Baseline up to end of therapy visit (up to 44 days)	

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: Since the study was not powered for efficacy, inferential statistical analyses were neither planned nor performed for this endpoint.

End point values	Daptomycin (1-6 years) - Safety	Daptomycin (7-11 years) - Safety	Daptomycin (12-17 years) - Safety	Comparator (1-6 years) - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	19	14	10
Units: Percentage of Participants				
number (not applicable)	18.2	0	28.6	20

End point values	Comparator (7-11 years) - Safety	Comparator (12-17 years) - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	7		
Units: Percentage of Participants				
number (not applicable)	0	14.3		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Abnormal Focused (Peripheral) Neurological Assessments at Test of Cure (TOC)

End point title	Number of Participants with Abnormal Focused (Peripheral) Neurological Assessments at Test of Cure (TOC) ^[5]
End point description: Focused neurological examinations were done at baseline, twice weekly during i.v. study drug, at the End of Therapy (i.v.) visit and at the TOC/Safety Visit. The focused neurological examinations include assessments of sensation, pupillary reflex and tracking, peripheral reflexes (biceps, patellar tendon, ankle jerk and plantar response), muscle tone and strength (upper and lower limbs), coordination (finger to nose) and tremor of the hands/fingers. Safety Population: includes all participants who receive any dose of i.v. study medication (daptomycin or SOC); participants are categorized by actual treatment received, irrespective of the randomization assignment.	
End point type	Primary
End point timeframe: TOC Safety Visit (up to 56 days)	

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: Since the study was not powered for efficacy, inferential statistical analyses were neither planned nor performed for this endpoint.

End point values	Daptomycin (1-6 years) - Safety	Daptomycin (7-11 years) - Safety	Daptomycin (12-17 years) - Safety	Comparator (1-6 years) - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	19	14	10
Units: Participants				
Alertness	0	0	0	0
Pupillary Reflex and Tracking	0	1	0	0
Peripheral Reflex - Biceps	0	0	0	0
Peripheral Reflex - Patellar Tendon	0	1	0	0
Peripheral Reflex - Ankle Jerk	0	1	0	0
Peripheral Reflex - Plantar Response	0	0	0	0
Muscle Tone - Lower/Upper Limbs	0	0	2	0
Muscle Strength - Lower/Upper Limbs	0	0	2	0
Coordination - (Finger to Nose)	0	0	0	0
Tremor of the hands/fingers	0	1	0	0
Sensation	0	0	0	0

End point values	Comparator (7-11 years) - Safety	Comparator (12-17 years) - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	7		
Units: Participants				
Alertness	0	0		
Pupillary Reflex and Tracking	0	0		
Peripheral Reflex - Biceps	0	0		
Peripheral Reflex - Patellar Tendon	0	0		
Peripheral Reflex - Ankle Jerk	0	0		
Peripheral Reflex - Plantar Response	0	0		
Muscle Tone - Lower/Upper Limbs	0	0		
Muscle Strength - Lower/Upper Limbs	0	0		
Coordination - (Finger to Nose)	0	0		
Tremor of the hands/fingers	0	0		
Sensation	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentration of Daptomycin

End point title	Trough Plasma Concentration of Daptomycin
-----------------	-------------------------------------------

End point description:

Plasma concentrations summarized were measured on Days 3 through 5 of i.v. dosing. Trough concentrations were those collected 22 to 26 hours following the end of the previous day's end of infusion and before the next infusion. Concentration values below the limit of quantification were excluded. The Exposure Response Population consists of any participant with at least one trough sample.

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

End point timeframe:

Days 3, 4 or 5 of treatment at pre-dose

End point values	Daptomycin (1-6 years) - ER	Daptomycin (7-11 years) - ER	Daptomycin (12-17 years) - ER	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	10	7	
Units: µg/mL				
arithmetic mean (standard deviation)	4.72 (± 1.643)	6.39 (± 3.035)	14.69 (± 19.109)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (C_{max}) of Daptomycin

End point title	Maximum Plasma Concentration (C _{max}) of Daptomycin
-----------------	----------------------------------------------------------------

End point description:

Plasma concentrations summarized were measured on Days 3 through 7 of i.v. dosing. Peak concentrations were those collected up to 15 minutes following the end of infusion. Concentration values below the limit of quantification were excluded. The Exposure Response Population consists of any participant with at least one peak sample.

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

End point timeframe:

Days 3, 4 or 5 of treatment at end of infusion

End point values	Daptomycin (1-6 years) - ER	Daptomycin (7-11 years) - ER	Daptomycin (12-17 years) - ER	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	18	8	
Units: µg/mL				
arithmetic mean (standard deviation)	96.69 (± 32.946)	87.66 (± 34.992)	74.7 (± 34.909)	

Statistical analyses

Secondary: Percentage of Participants with Clinical Success at TOC Visit

End point title	Percentage of Participants with Clinical Success at TOC Visit
-----------------	---------------------------------------------------------------

End point description:

This is the Investigator's assessment of clinical response at TOC/Safety Visit with regard to the determination of the resolution/improvement of signs and symptoms. An assessment of cure or improved is considered clinical success. Cure: resolution of clinically significant signs and symptoms associated with admission infection; no further antibiotic therapy is required for the primary infection under study. Improvement: partial resolution of clinical signs/symptoms of infection such that no further antibiotic therapy is required for the primary infection under study. The mMITT population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven *S. aureus* bacteremia at baseline.

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

End point timeframe:

7-14 days after the last dose of study medication (up to 56 days)

End point values	Daptomycin (1-6 years) - mMITT	Daptomycin (7-11 years) - mMITT	Daptomycin (12-17 years) - mMITT	Comparator (1-6 years) - mMITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	17	14	8
Units: Percentage of Participants				
number (not applicable)				
Cure	80	94.1	78.6	87.5
Improved	5	0	7.1	0

End point values	Comparator (7-11 years) - mMITT	Comparator (12-17 years) - mMITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	5		
Units: Percentage of Participants				
number (not applicable)				
Cure	77.8	60		
Improved	0	0		

Statistical analyses

Statistical analysis title	Daptomycin vs. Comparator: 1-6 years
----------------------------	--------------------------------------

Statistical analysis description:

Difference in satisfactory response between treatment groups (Daptomycin - Comparator). Satisfactory response = cured + improved.

Comparison groups	Daptomycin (1-6 years) - mMITT v Comparator (1-6 years) - mMITT
-------------------	-----------------------------------------------------------------

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.3
upper limit	25.3

Statistical analysis title	Daptomycin vs. Comparator: 7-11 years
-----------------------------------	---------------------------------------

Statistical analysis description:

Difference in satisfactory response between treatment groups (Daptomycin - Comparator). Satisfactory response = cured + improved.

Comparison groups	Daptomycin (7-11 years) - mMITT v Comparator (7-11 years) - mMITT
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	45.7

Statistical analysis title	Daptomycin vs. Comparator: 12-17 years
-----------------------------------	----------------------------------------

Statistical analysis description:

Difference in satisfactory response between treatment groups (Daptomycin - Comparator). Satisfactory response = cured + improved.

Comparison groups	Daptomycin (12-17 years) - mMITT v Comparator (12-17 years) - mMITT
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	25.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	72.4

Secondary: Percentage of Participants with Overall Success at TOC Visit

End point title	Percentage of Participants with Overall Success at TOC Visit
End point description: Overall success is based on microbiologic responses after initiating study drug and clinical response at TOC/Safety Visit. Overall outcome is a success if both clinical and microbiologic outcomes are successes. An assessment of cure or improved is considered clinical success. Microbiological Success: a participant for whom all baseline infecting pathogens were eradicated (presumed or documented) within 7 days from the start of study drug for uncomplicated bacteremia with no source of infection present, and 10 days for complicated bacteremia or when the source of infection has not been removed. The mMITT population is composed of all randomized and treated participants who received ≥ 1 dose of study drug and who had proven <i>S. aureus</i> bacteremia at baseline.	
End point type	Secondary
End point timeframe: 7-14 days after the last dose of study medication (up to 56 days)	

End point values	Daptomycin (1-6 years) - mMITT	Daptomycin (7-11 years) - mMITT	Daptomycin (12-17 years) - mMITT	Comparator (1-6 years) - mMITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	17	14	8
Units: Percentage of Participants				
number (not applicable)				
Overall Success	80	82.4	50	75

End point values	Comparator (7-11 years) - mMITT	Comparator (12-17 years) - mMITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	5		
Units: Percentage of Participants				
number (not applicable)				
Overall Success	44.4	60		

Statistical analyses

Statistical analysis title	Daptomycin vs. Comparator: 1-6 years
Statistical analysis description: Difference in success response between treatment arms (Daptomycin - Comparator).	
Comparison groups	Daptomycin (1-6 years) - mMITT v Comparator (1-6 years) - mMITT
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.8
upper limit	39.8

Statistical analysis title	Daptomycin vs. Comparator: 7-11 years
Statistical analysis description:	
Difference in success response between treatment arms (Daptomycin - Comparator).	
Comparison groups	Daptomycin (7-11 years) - mMITT v Comparator (7-11 years) - mMITT
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	37.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	75.1

Statistical analysis title	Daptomycin vs. Comparator: 12-17 years
Statistical analysis description:	
Difference in success response between treatment arms (Daptomycin - Comparator).	
Comparison groups	Daptomycin (12-17 years) - mMITT v Comparator (12-17 years) - mMITT
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference (%)
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.3
upper limit	40.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Administration of first dose through the last follow-up visit (up to 77 days)

Adverse event reporting additional description:

Safety Population - includes all participants who received any dose of i.v. study medication (daptomycin or standard of care comparator). Participants in the safety population were categorized by actual treatment received, irrespective of the randomization assignment.

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

Dictionary used

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

Dictionary version	17.1
--------------------	------

Reporting groups

Reporting group title	Daptomycin 12 mg/kg (1-6 yrs)
-----------------------	-------------------------------

Reporting group description:

Participants aged 1-6 years were administered daptomycin 12 mg/kg, infused once daily, intravenously, over 60 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. AEs and SAEs were collected from first dose of study medication through last follow-up visit from participants on i.v. and/or oral medication.

Reporting group title	Comparator (1-6 yrs)
-----------------------	----------------------

Reporting group description:

Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. AEs and SAEs were collected from first dose of study medication through last follow-up visit from participants on i.v. and/or oral medication.

Reporting group title	Daptomycin 9 mg/kg (7-11 yrs)
-----------------------	-------------------------------

Reporting group description:

Participants aged 7-11 years were administered daptomycin 9 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. AEs and SAEs were collected from first dose of study medication through last follow-up visit from participants on i.v. and/or oral medication.

Reporting group title	Comparator (7-11 yrs)
-----------------------	-----------------------

Reporting group description:

Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-28 days. AEs and SAEs were collected from first dose of study medication through last follow-up visit from participants on i.v. and/or oral medication.

Reporting group title	Daptomycin 7 mg/kg (12-17 yrs)
-----------------------	--------------------------------

Reporting group description:

Participants aged 12-17 were administered daptomycin 7 mg/kg, infused once daily, intravenously, over 30 minutes; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days. AEs and SAEs were collected from first dose of study medication through last follow-up visit from participants on i.v. and/or oral medication.

Reporting group title	Comparator (12-17 yrs)
-----------------------	------------------------

Reporting group description:

Recommended as i.v. vancomycin or semi-synthetic penicillin or first-generation cephalosporins or clindamycin, given as per local guidelines or site-specific prescribing information; therapy duration (uncomplicated bacteremia) = 5-28 days, therapy duration (complicated bacteremia) = 7-42 days. AEs and SAEs were collected from first dose of study medication through last follow-up visit from participants on i.v. and/or oral medication.

Serious adverse events	Daptomycin 12 mg/kg (1-6 yrs)	Comparator (1-6 yrs)	Daptomycin 9 mg/kg (7-11 yrs)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	2 / 10 (20.00%)	4 / 19 (21.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 22 (4.55%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 22 (4.55%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	0 / 19 (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
General disorders and administration site conditions			
Device breakage			
subjects affected / exposed	1 / 22 (4.55%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Intestine transplant rejection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (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

Pneumothorax			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (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
Respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone fistula			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (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
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	0 / 19 (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
Bacteraemia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscle abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (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 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (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
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Comparator (7-11 yrs)	Daptomycin 7 mg/kg (12-17 yrs)	Comparator (12-17 yrs)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	3 / 14 (21.43%)	2 / 7 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
Vascular disorders			
Venous thrombosis limb			

subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
General disorders and administration site conditions			
Device breakage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
Immune system disorders			
Intestine transplant rejection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
Pulmonary oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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			
Bone fistula			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
Synovitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	0 / 7 (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			
Arthritis bacterial			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
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 / 9 (0.00%)	1 / 14 (7.14%)	0 / 7 (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
Bone abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
Muscle abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	0 / 7 (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
Osteomyelitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	0 / 7 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (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

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

Non-serious adverse events	Daptomycin 12 mg/kg (1-6 yrs)	Comparator (1-6 yrs)	Daptomycin 9 mg/kg (7-11 yrs)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 22 (40.91%)	6 / 10 (60.00%)	11 / 19 (57.89%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Thrombophlebitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter site discharge			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Catheter site oedema			

subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Catheter site pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Device breakage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Infusion site pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	3	1	1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Epididymal cyst			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	1 / 22 (4.55%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Hypoxia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Pharyngeal ulceration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Pulmonary mass			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Wheezing subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Blood potassium decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Blood sodium decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Body temperature increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	0 / 19 (0.00%) 0
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Transaminases increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Contusion			

subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Excoriation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Wound dehiscence			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 22 (4.55%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Thrombocytosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eye disorders			

Vision blurred subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Diarrhoea subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4	1 / 10 (10.00%) 1	1 / 19 (5.26%) 1
Nausea subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	1 / 19 (5.26%) 1
Vomiting subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	2 / 10 (20.00%) 4	2 / 19 (10.53%) 4
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Decubitus ulcer subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	1 / 19 (5.26%) 1
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Rash erythematous			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	0 / 19 (0.00%) 0
Rash macular subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	0 / 19 (0.00%) 0
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	0 / 19 (0.00%) 0
Skin exfoliation subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Pollakiuria subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Renal failure acute subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Renal necrosis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Haemarthrosis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Myositis			

subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Arthritis bacterial			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Infected skin ulcer			
subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Lung abscess			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 10 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Osteomyelitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 10 (10.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0

Osteomyelitis acute subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	0 / 19 (0.00%) 0
Postoperative wound infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Rash pustular subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Rhinovirus infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Systemic candida subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Varicella subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 10 (10.00%) 1	0 / 19 (0.00%) 0
Metabolism and nutrition disorders			
Fluid overload subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	1 / 19 (5.26%) 1
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0
Hyperphosphataemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 10 (0.00%) 0	0 / 19 (0.00%) 0

Non-serious adverse events	Comparator (7-11 yrs)	Daptomycin 7 mg/kg (12-17 yrs)	Comparator (12-17 yrs)
-----------------------------------	-----------------------	--------------------------------	------------------------

Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 9 (100.00%)	8 / 14 (57.14%)	5 / 7 (71.43%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Phlebitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site discharge			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Catheter site oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Device breakage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infusion site pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	2 / 14 (14.29%)	0 / 7 (0.00%)
occurrences (all)	3	2	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			

Epididymal cyst subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1
Respiratory, thoracic and mediastinal disorders			
Atelectasis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Hypoxia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Pharyngeal ulceration subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Pulmonary mass subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Wheezing subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Psychiatric disorders			
Abnormal behaviour subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0
Blood potassium decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0

Blood sodium decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Body temperature increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Transaminases increased subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Excoriation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Wound subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Wound dehiscence subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Cardiac disorders			
Ventricular extrasystoles subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1

Lethargy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Blood and lymphatic system disorders			
Abdominal lymphadenopathy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Anaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 2
Thrombocytosis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Eye disorders			
Vision blurred subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 14 (14.29%) 2	0 / 7 (0.00%) 0
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0

Decubitus ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	2 / 9 (22.22%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash erythematous			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal failure acute			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Renal necrosis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Haemarthrosis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Myositis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Neck pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	1 / 7 (14.29%) 1
Infections and infestations			
Abdominal abscess subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Abscess subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Arthritis bacterial subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Candida infection			

subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infected skin ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lung abscess			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Osteomyelitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Osteomyelitis acute			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Postoperative wound infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rash pustular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinovirus infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Systemic candida			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Varicella			

subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypernatraemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	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