

**Clinical trial results:****A Multicenter, Randomized, Double-Blinded Comparative Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Daptomycin Versus Active Comparator in Pediatric Subjects With Acute Hematogenous Osteomyelitis Due to Gram-Positive Organisms
Summary**

EudraCT number	2013-000864-28
Trial protocol	DE HU IT ES GR LV GB EE BG FR SI Outside EU/EEA
Global end of trial date	20 December 2016

Results information

Result version number	v1 (current)
This version publication date	18 June 2017
First version publication date	18 June 2017

Trial information**Trial identification**

Sponsor protocol code	3009-006
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01922011
WHO universal trial number (UTN)	-
Other trial identifiers	Cubist: DAP-PEDOST-11-03

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
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 December 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to determine whether daptomycin is effective and safe in the treatment of pediatric participants with Acute Hematogenous Osteomyelitis (AHO) when compared to vancomycin (or equivalent) or nafcillin (or β -lactam equivalent). The primary hypothesis is that daptomycin is non-inferior compared with vancomycin (or equivalent) or nafcillin (or β -lactam equivalent) with respect to improvement in Pain, Inflammation, and Limb Function on or before study Day 5.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2013
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: 2
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Ukraine: 31

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	149
EEA total number of subjects	48

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)	8
Children (2-11 years)	94
Adolescents (12-17 years)	47
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:

Pediatric participants from ages 1 year to < 18 years with acute hematogenous osteomyelitis (AHO) were enrolled in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Daptomycin

Arm description:

Intravenous (IV) daptomycin 7, 9, or 12 mg/kg once daily and ≤3 dummy infusions daily

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

Dosage and administration details:

IV daptomycin Infusion A in 12 to <18 years old (7 mg/kg); in 7 to < 12 year olds (9 mg/kg); in 24 months to <7 year olds (12 mg/kg); in 12 to <24 month olds (12 mg/kg). Infused over 60 minutes ± 10 minutes once daily followed by up to 3 dummy infusions q6h infused over 60 (± 10) min to maintain the blind.

Arm title	Vancomycin or Nafcillin
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Arm description:

IV vancomycin (or equivalent), 10 to 15 mg/kg every six hours (q6h) or IV nafcillin (or β-lactam equivalent) 100-200 mg/kg/day, in divided doses q6h

Arm type	Active comparator
Investigational medicinal product name	Nafcillin (or equivalent)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV nafcillin (or β-lactam equivalent) (Infusions A,B,C,D) at 100-200 mg/kg/day, in divided doses infused over 60 (± 10) min q6h (± 1 hour)

Investigational medicinal product name	Vancomycin (or equivalent)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV vancomycin (or equivalent) (Infusions A,B,C,D), 10 to 15 mg/kg, infused over 60 (± 10) minutes q6h

(± 1 hour)

Number of subjects in period 1	Daptomycin	Vancomycin or Nafcillin
Started	75	74
Completed	69	69
Not completed	6	5
Randomized in error	1	-
Physician decision	-	1
Not Treated	1	-
Parent/Guardian Decision	3	-
Lack of willing home health agency	1	-
Missed Test-of-Cure Visit	-	2
Lost to follow-up	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Daptomycin
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Reporting group description:

Intravenous (IV) daptomycin 7, 9, or 12 mg/kg once daily and ≤ 3 dummy infusions daily

Reporting group title	Vancomycin or Nafcillin
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Reporting group description:

IV vancomycin (or equivalent), 10 to 15 mg/kg every six hours (q6h) or IV nafcillin (or β -lactam equivalent) 100-200 mg/kg/day, in divided doses q6h

Reporting group values	Daptomycin	Vancomycin or Nafcillin	Total
Number of subjects	75	74	149
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	5	3	8
Children (2-11 years)	46	48	94
Adolescents (12-17 years)	24	23	47
Age Continuous Units: years			
arithmetic mean	9.1	9.2	-
standard deviation	± 4.4	± 4.1	-
Gender Categorical Units: Subjects			
Female	31	25	56
Male	44	49	93

End points

End points reporting groups

Reporting group title	Daptomycin
Reporting group description: Intravenous (IV) daptomycin 7, 9, or 12 mg/kg once daily and ≤ 3 dummy infusions daily	
Reporting group title	Vancomycin or Nafcillin
Reporting group description: IV vancomycin (or equivalent), 10 to 15 mg/kg every six hours (q6h) or IV nafcillin (or β -lactam equivalent) 100-200 mg/kg/day, in divided doses q6h	
Subject analysis set title	Daptomycin 12 - < 24 months old
Subject analysis set type	Sub-group analysis
Subject analysis set description: IV daptomycin 12 mg/kg once daily and ≤ 3 dummy infusions daily for ages 12 - < 24 months old only.	
Subject analysis set title	Daptomycin 24 months - < 7 yrs old
Subject analysis set type	Sub-group analysis
Subject analysis set description: IV daptomycin 12 mg/kg once daily and ≤ 3 dummy infusions daily for ages 24 months - < 7 yrs old only.	
Subject analysis set title	Daptomycin 7 - < 12 yrs old
Subject analysis set type	Sub-group analysis
Subject analysis set description: IV daptomycin 9, mg/kg once daily and ≤ 3 dummy infusions daily for ages 7 - < 12 yrs old only.	
Subject analysis set title	Daptomycin 12 - < 18 yrs old
Subject analysis set type	Sub-group analysis
Subject analysis set description: IV daptomycin 7 mg/kg once daily and ≤ 3 dummy infusions daily for ages 12 - < 18 yrs old only.	

Primary: Percentage of participants with clinical improvement in the 3 general categories of Pain, Inflammation, and Limb Function based on the Investigator's overall assessment of severity of each of the symptom categories by study day 5.

End point title	Percentage of participants with clinical improvement in the 3 general categories of Pain, Inflammation, and Limb Function based on the Investigator's overall assessment of severity of each of the symptom categories by study day 5.
End point description: Clinical improvement was based on the Investigator's overall assessment of severity based on the following definition: If 3 general categories are present at baseline: at least a 1-point improvement (i.e. severe to moderate, moderate to mild, mild to absent) in at least 2 and no worsening in the other. If 2 general categories are present at baseline: at least a 2-point improvement (i.e. severe to mild, moderate to absent) in at least 1 and no worsening or new findings in the others OR at least a 1-point improvement in both and no new findings in the other. If 1 general category is present at baseline: at least a 2-point improvement (i.e., severe to mild, moderate to absent) and no new findings in the others. All randomized participants who received any amount of IV study drug and who had a confirmed or suspected diagnosis of AHO, excluding those with confirmed culture of a gram-negative organism from any baseline specimen.	
End point type	Primary
End point timeframe: Up to study Day 5	

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	70		
Units: Percentage of participants				
number (confidence interval 95%)	77.5 (67.7 to 87.2)	82.9 (74 to 91.7)		

Statistical analyses

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin
Statistical analysis description: 95% confidence interval of the common difference was based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.	
Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.421
Method	Wald
Parameter estimate	Common Difference
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.4
upper limit	7.4

Notes:

[1] - Non-inferiority was concluded if the lower bound of the 2-sided 95% CI is greater than -15%

Secondary: Percentage of participants with clinical improvement measured as a composite end point of pain, inflammation, limb function, body temperature, and C-reactive protein at End-of IV (EOIV) therapy visit.

End point title	Percentage of participants with clinical improvement measured as a composite end point of pain, inflammation, limb function, body temperature, and C-reactive protein at End-of IV (EOIV) therapy visit.
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End point description:

A participant had a favorable outcome in this composite endpoint if all 3 of the following criteria were met: Clinical improvement in the general symptom categories of Pain, Inflammation, and Limb Function on or before Study Day 5; Body temperature $\leq 38^{\circ}\text{C}$ (100.4°F) over the preceding 24 hours; and C-reactive Protein (CRP) decreased from baseline for participants who had a baseline CRP $>\text{ULN}$ (upper limit of normal)) or remain $\leq\text{ULN}$ for participants who had a baseline $\leq\text{ULN}$ on or before Study Day 5. The EOIV visit is within 24 hours after the last dose of IV study drug and before switch to optional open label (PO) therapy, if applicable. All randomized participants who received any amount of IV study drug and who had a confirmed diagnosis of AHO (Categories I, II and III), excluding participants with confirmed culture of a gram negative organism from any baseline specimen, and who did not have all clinical assessments performed at the time point.

End point type	Secondary
End point timeframe:	
End of IV treatment"	

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Percentage of participants				
number (confidence interval 95%)	71 (60.3 to 81.7)	76.5 (66.4 to 86.6)		

Statistical analyses

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin
Statistical analysis description:	
95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.	
Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.467
Method	Wald
Parameter estimate	Common difference
Point estimate	-7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.6
upper limit	7.9

Secondary: Percentage of participants with a favorable clinical outcome

End point title	Percentage of participants with a favorable clinical outcome
End point description:	
Favorable clinical outcomes are clinical recovery and clinical cure. Clinical cure is resolution of all acute symptoms of AHO or improvement where no further intravenous antibacterial therapy is required. Clinical recovery is defined as clinical improvement in the composite end point three general categories of Pain, Inflammation, and Limb Function on or before Study Day 5, and no development of new symptoms of AHO; body temperature $\leq 38^{\circ}\text{C}$ (100.4°F) for 24 hours; no new or additional infection such that no further antibacterial therapy or surgery are required; no hematogenous metastatic infection or bacteremia. The End of Therapy (EOT) visit is within 48 hours of last dose of PO therapy. All randomized participants who received any amount of IV study drug and who had a confirmed diagnosis of AHO (Categories I, II and III), excluding participants with confirmed culture of a gram-negative organism from any baseline specimen.	
End point type	Secondary
End point timeframe:	
Baseline (within 48 hours prior to first dose of IV study drug) - and up to Test of Cure (21-35 days after last dose of IV study drug) (up to Day 77)	

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	70		
Units: Percentage of participants				
number (confidence interval 95%)				
At End of IV (EOIV) Therapy (n= 71,69)	85.9 (77.8 to 94)	91.3 (84.7 to 98)		
At End of Therapy (EOT) (n= 71,69)	83.1 (74.4 to 91.8)	89.9 (82.7 to 97)		
At Test Of Cure (TOC) (n= 71,70)	81.7 (72.7 to 90.7)	87.1 (79.3 to 95)		

Statistical analyses

Statistical analysis title	At EOIV visit
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Statistical analysis description:

95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.

Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.313
Method	Wald
Parameter estimate	Common difference
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	5

Statistical analysis title	At EOT visit
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Statistical analysis description:

95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.

Comparison groups	Daptomycin v Vancomycin or Nafcillin
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Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.239
Method	Wald
Parameter estimate	Common difference
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	4

Statistical analysis title	At TOC visit
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Statistical analysis description:

95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor

Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.37
Method	Wald
Parameter estimate	Common difference
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.1
upper limit	5.8

Secondary: Percentage of participants with a clinical cure categorized by baseline pathogen at Test of Cure

End point title	Percentage of participants with a clinical cure categorized by baseline pathogen at Test of Cure
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End point description:

At Test Of Cure (TOC) clinical cure is resolution of all acute symptoms of AHO or improvement where no further antibacterial therapy is required. Favorable microbiological outcomes are where the the original baseline pathogen was absent; or where the source specimen was not available to culture, and the participant was assessed as a clinical cure. For a favorable microbiological response, the outcome for each participant's baseline pathogen must be eradicated or presumed eradicated. Other pathogens include Arcanobacterium haemolyticum, Gram positive cocci, Staphylococcus epidermidis, Streptococcus (Strep.) dysgalactiae, Strep. mitis group and Strep. pyogenes. All randomized participants who received IV study drug and had a confirmed diagnosis of AHO, excluding participants with confirmed culture of a gram-negative organism; but including those where at least one bacterial pathogen was isolated from an appropriate microbiological specimen at baseline.

End point type	Secondary
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End point timeframe:

Baseline (within 48 hours prior to first dose of IV study drug) - and Test of Cure (21-35 days after last

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: Percentage of participants				
number (confidence interval 95%)				
Overall Baseline Infecting Pathogen (n =45,47)	77.8 (65.6 to 89.9)	87.2 (77.7 to 96.8)		
Staphylococcus Aureus (SA) (n= 43,42)	76.7 (64.1 to 89.4)	88.1 (78.3 to 97.9)		
Methicillin Susceptible SA (MSSA) (n= 39,37)	79.5 (66.8 to 92.2)	94.6 (87.3 to 100)		
Methicillin Resistant SA (MRSA) (n= 4,4)	50 (1 to 99)	25 (0 to 67.4)		
Other Pathogens (n= 2,7)	100 (100 to 100)	85.7 (59.8 to 100)		

Statistical analyses

Statistical analysis title	Overall Baseline Infecting Pathogen
Statistical analysis description:	
95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.	
Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23
Method	Wald
Parameter estimate	Common difference
Point estimate	-10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.3
upper limit	5.4

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin SA
Statistical analysis description:	
95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.	
Comparison groups	Daptomycin v Vancomycin or Nafcillin

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.164
Method	Wald
Parameter estimate	Common difference
Point estimate	-12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.5
upper limit	4.4

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin MSSA
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Statistical analysis description:

95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.

Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.043
Method	Wald
Parameter estimate	Common difference
Point estimate	-15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.2
upper limit	1.1

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin MRSA
Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.45
Method	Wald

Statistical analysis title	Other Pathogen
Comparison groups	Daptomycin v Vancomycin or Nafcillin

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.28
Method	Wald

Secondary: Percentage of participants with sustained clinical improvement

End point title	Percentage of participants with sustained clinical improvement
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End point description:

Sustained clinical improvement was defined as participants with clinical improvement who further met the definition of clinical cure. Clinical improvement was in the three general categories of Pain, Inflammation, and Limb Function on or before Study Day 5. Clinical cure is defined as resolution of all acute symptoms of AHO or improvement to such an extent that no further intravenous antibacterial therapy is required. The EOT visit is within 48 hours of last dose of PO therapy. All randomized participants who received any amount of IV study drug and who had a confirmed or suspected diagnosis of AHO, excluding those with confirmed culture of a gram negative organism from any baseline specimen; and had non-missing clinical outcome.

End point type	Secondary
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End point timeframe:

Baseline (within 48 hours prior to first dose of IV study drug) - up to Test of Cure (21-35 days after last dose of IV study drug) (up to Day 77)

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	70		
Units: Percentage of participants				
number (confidence interval 95%)				
EOT (n= 55,57)	89.1 (80.9 to 97.3)	94.7 (88.9 to 100)		
TOC (n= 55,58)	87.3 (78.5 to 96.1)	91.4 (84.2 to 98.6)		

Statistical analyses

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin at EOT
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Statistical analysis description:

95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.

Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.272
Method	Wald
Parameter estimate	Common difference
Point estimate	-6.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.2
upper limit	5.5

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin at TOC
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Statistical analysis description:

95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.

Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.48
Method	Wald
Parameter estimate	Common difference
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	7.9

Secondary: Percentage of participants with a favorable microbiological response categorized by baseline pathogen at Test of Cure

End point title	Percentage of participants with a favorable microbiological response categorized by baseline pathogen at Test of Cure
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End point description:

Favorable microbiological outcomes are either eradication where the source specimen demonstrated absence of the original baseline pathogen; or presumed eradication where the source specimen was not available to culture, and the participant was assessed as a clinical cure. For a favorable microbiological response, the outcome for each baseline pathogen must be eradicated or presumed eradicated. Other pathogens include Arcanobacterium haemolyticum, Gram positive cocci, Staphylococcus epidermidis, Streptococcus dysgalactiae, Streptococcus mitis group and Streptococcus pyogenes. All randomized participants who received IV study drug and had a confirmed diagnosis of AHO, excluding participants with confirmed culture of a gram negative organism; but including those where at least one bacterial pathogen was isolated from an appropriate microbiological specimen at baseline.

End point type	Secondary
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End point timeframe:

Baseline (within 48 hours prior to first dose of IV study drug) - and Test of Cure (21-35 days after last dose of IV study drug) (up to Day 77)

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: Percentage of participants				
number (confidence interval 95%)				
Overall Baseline Infecting Pathogen (n =45,47)	82.2 (71.1 to 93.4)	91.5 (83.5 to 99.5)		
SA (n= 43,42)	81.4 (69.8 to 93)	92.9 (85.1 to 100)		
MSSA (n= 39,37)	84.6 (73.3 to 95.9)	94.6 (87.3 to 100)		
MRSA (n= 4,4)	50 (1 to 99)	75 (32.6 to 100)		
Other Pathogens (n= 2,7)	100 (100 to 100)	85.7 (59.8 to 100)		

Statistical analyses

Statistical analysis title	Overall Baseline Infecting Pathogen
Statistical analysis description: 95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.	
Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Common difference
Point estimate	-10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.8
upper limit	4.2

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin SA
Statistical analysis description: 95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.	
Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Common difference
Point estimate	-12.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.2
upper limit	2.8

Statistical analysis title	Daptomycin vs Vancomycin or Nafcillin MSSA
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Statistical analysis description:

95% confidence interval of the common difference (Daptomycin minus Vancomycin or Nafcillin) is based on stratified Newcombe confidence interval (CI) with minimum risk weights, with age cohort as the stratification factor.

Comparison groups	Daptomycin v Vancomycin or Nafcillin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Common difference
Point estimate	-10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.4
upper limit	5.2

Other pre-specified: Number of participants with 1 or more Adverse Events (AEs)

End point title	Number of participants with 1 or more Adverse Events (AEs)
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End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, clinically significant laboratory finding, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Treated participants based on the treatment received.

End point type	Other pre-specified
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End point timeframe:

Administration of first dose up to approximately six and a half months after last dose of study drug

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: Participants				
number (not applicable)	34	45		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of participants with 1 or more Serious Adverse Events (SAEs)

End point title	Number of participants with 1 or more Serious Adverse Events (SAEs)
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End point description:

An SAE is any untoward medical occurrence that at any dose results in death; is life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect. Treated participants based on the treatment received.

End point type	Other pre-specified
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End point timeframe:

Administration of first dose through the last follow-up visit; an expected time of up to 6.5 months

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: Participants				
number (not applicable)	5	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Concentration of serum creatine kinase (CK)

End point title	Concentration of serum creatine kinase (CK)
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End point description:

Serum was collected at Baseline and at End of Therapy IV, from which the concentration of CK was determined.

End point type	Other pre-specified
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End point timeframe:

Baseline and End of Therapy IV (up to Day 42)

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	72		
Units: U/L				
arithmetic mean (standard deviation)				
Baseline (n = 68,72)	141.7 (± 188.7)	99.9 (± 95)		
End of Therapy IV (n= 35,41)	89.4 (± 66.55)	82.4 (± 95.03)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in number of participants with abnormal focused (peripheral) neurological assessments

End point title	Change from baseline in number of participants with abnormal focused (peripheral) neurological assessments
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End point description:

Focused neurological examinations include assessments of alertness, 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.

End point type	Other pre-specified
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End point timeframe:

Baseline and up to Test of Cure (21-35 days after last dose of IV study drug) (up to Day 77)

End point values	Daptomycin	Vancomycin or Nafcillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Participants				
number (not applicable)				

Notes:

[2] - Data were only summarized for each visit; but not analyzed.

[3] - Data were only summarized for each visit; but not analyzed.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma concentration of daptomycin at the end of IV infusion

End point title	Plasma concentration of daptomycin at the end of IV infusion
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End point description:

Blood samples were collected, after infusion of IV study drug between the end of infusion on study day 3, up to Day 42. Participants who received a known amount of daptomycin and who had at least one blood sample collected. Participants treated with vancomycin, nafcillin or equivalent were not analyzed.

End point type	Other pre-specified
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End point timeframe:

Day 3 up to Day 42

End point values	Daptomycin 12 - < 24 months old	Daptomycin 24 months - < 7 yrs old	Daptomycin 7 - < 12 yrs old	Daptomycin 12 - < 18 yrs old
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	6	5	10
Units: µg/mL				
arithmetic mean (standard deviation)	36.8 (± 0)	75.772 (± 39.1156)	58.94 (± 27.4149)	68.907 (± 56.6695)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma concentration of daptomycin at 15 minutes to 1 hour after the end of IV infusion

End point title	Plasma concentration of daptomycin at 15 minutes to 1 hour after the end of IV infusion
End point description:	Blood samples were collected, after infusion of IV study drug between the end of infusion on study day 3, up to Day 42. Participants who received a known amount of daptomycin and who had at least one blood sample collected. Participants treated with vancomycin, nafcillin or equivalent were not analyzed.
End point type	Other pre-specified
End point timeframe:	Day 3 up to Day 42

End point values	Daptomycin 12 - < 24 months old	Daptomycin 24 months - < 7 yrs old	Daptomycin 7 - < 12 yrs old	Daptomycin 12 - < 18 yrs old
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	8	12	10
Units: µg/mL				
arithmetic mean (standard deviation)	65.533 (± 30.8468)	84.564 (± 35.0179)	70.342 (± 35.0196)	57.37 (± 61.5616)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma concentration of daptomycin at 2 to 3 hours after the end of IV

End point title	Plasma concentration of daptomycin at 2 to 3 hours after the end of IV
End point description:	Participants who received a known amount of daptomycin and who had at least one blood sample collected. Participants treated with vancomycin, nafcillin or equivalent were not analyzed.
End point type	Other pre-specified
End point timeframe:	Day 3 up to Day 42

End point values	Daptomycin 12 - < 24 months old	Daptomycin 24 months - < 7 yrs old	Daptomycin 7 - < 12 yrs old	Daptomycin 12 - < 18 yrs old
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[4]	6	5	9
Units: µg/mL				
arithmetic mean (standard deviation)	()	51.15 (± 16.1179)	31.2 (± 14.7027)	46.756 (± 51.2678)

Notes:

[4] - Values were treated as missing, as concentrations were below the limit of quantification.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma concentration of daptomycin at 4 to 5 hours after the end of IV infusion

End point title	Plasma concentration of daptomycin at 4 to 5 hours after the end of IV infusion
End point description:	Participants who received a known amount of daptomycin and who had at least one blood sample collected. Participants treated with vancomycin, nafcillin or equivalent were not analyzed.
End point type	Other pre-specified
End point timeframe:	Day 3 up to Day 42

End point values	Daptomycin 12 - < 24 months old	Daptomycin 24 months - < 7 yrs old	Daptomycin 7 - < 12 yrs old	Daptomycin 12 - < 18 yrs old
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	7	11	10
Units: µg/mL				
arithmetic mean (standard deviation)	35.933 (± 6.3956)	53.059 (± 21.8879)	50.809 (± 26.0469)	41.447 (± 57.8657)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events (AEs): Up to approximately six and a half months after last dose of study drug.

Non-serious AEs (NSAEs): Up to 35 days after last dose of study drug

Adverse event reporting additional description:

Treated participants based on the treatment received

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Vancomycin or Nafcillin
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Reporting group description:

IV vancomycin (or equivalent), 10 to 15 mg/kg q6h, or IV nafcillin (or β -lactam equivalent) 100-200 mg/kg/day, in divided doses q6h

Reporting group title	Daptomycin
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Reporting group description:

IV daptomycin 7, 9, or 12 mg/kg once daily and ≤ 3 dummy infusions daily

Serious adverse events	Vancomycin or Nafcillin	Daptomycin	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 72 (5.56%)	5 / 74 (6.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red man syndrome			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 74 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Vancomycin or Nafcillin	Daptomycin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 72 (33.33%)	6 / 74 (8.11%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 72 (5.56%)	0 / 74 (0.00%)	
occurrences (all)	4	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 72 (6.94%)	2 / 74 (2.70%)	
occurrences (all)	6	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 72 (8.33%)	1 / 74 (1.35%)	
occurrences (all)	6	1	
Diarrhoea			
subjects affected / exposed	4 / 72 (5.56%)	1 / 74 (1.35%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	6 / 72 (8.33%)	3 / 74 (4.05%)	
occurrences (all)	6	3	

Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 5	1 / 74 (1.35%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 5	0 / 74 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2013	Amendment 1: Revised criteria for eligibility and discontinuations due to safety; clarified that local approved product information was to be used for the active comparator; and added a subsection about CPK elevations.
10 April 2014	Amendment 2: Added text about the timing of infusions to maintain the blind; and added a stepwise enrollment plan that began with participants aged 2 to <18 years then broadened enrollment to 12 months to <18 years of age after review by the Data Monitoring Committee. Other revisions clarified the maximum concentration of final diluted daptomycin, vancomycin dose adjustments, and clinical assessments for participants who remained hospitalized and on IV trial treatment after Study Day 5. Inclusion criteria were changed to clarify baseline disease parameters and to reflect stepwise enrollment.
08 September 2014	Amendment 3: Revised eligibility criteria, added teicoplanin as an alternative to vancomycin; clarified culture and induration specifications; added 2 antibiotics for the oral switch, and clarified blinding requirements. Clarified reference information for daptomycin, Keflex®, Cleocin®, Zyvox®, Bactrim®, Augmentin®, and vancomycin.
15 September 2015	Amendment 4: Included a decrease in the trial sample size, and changed the AE collection period. The AE reporting timeframe and SAE follow-up period were revised; text was added about CPK increases, and language was added to clarify that the IV comparators and oral antibiotics listed were recommendations. Inclusion criteria and an exclusion criterion were changed to include participants with suspect or confirmed AHO; better define AHO compared with chronic osteomyelitis, and allow pelvic AHO, respectively. Exclusion criterion was added to exclude subjects with suspected or confirmed pneumonia, empyema, meningitis, or endocarditis. The recommended length of IV trial treatment was revised to a minimum of 4 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported