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

## Summary

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

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 30 April 2016 |
| First version publication date | 05 August 2015 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 3009-017 |

**Additional study identifiers**

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

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 02 March 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 October 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 03 September 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | India: 123 |
| Country: Number of subjects enrolled | United States: 273 |
| Worldwide total number of subjects | 396 |
| EEA total number of subjects | 0 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 45 |
| Children (2-11 years) | 234 |
| Adolescents (12-17 years) | 117 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Daptomycin |

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|---|
| **Arm title** | Standard of Care (SOC) |

Arm description:

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

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Standard of Care |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

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

Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days.

Notes:

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

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

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

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Study (overall period) |
|---|---|

Reporting group description: -

| Reporting group values | Overall Study (overall period) | Total | |
|---|---|---|---|
| Number of subjects | 396 | 396 | |
| Age categorical<br>Units: Subjects | | | |
| Age continuous | | | |
| For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available. | | | |
| Units: years<br>arithmetic mean<br>standard deviation | <br>8.21<br>± 5.134 | <br><br>- | |
| Gender categorical | | | |
| Gender was not known for 7 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 188 | 188 | |
| Male | 208 | 208 | |

### Subject analysis sets

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

Subject analysis set description:

Subjects who received at least 1 dose of study drug.

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

Subject analysis set description:

Subjects who received at least 1 dose of study drug.

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

7 to 11 years

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

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

Subject analysis set description:

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

| **Reporting group values** | Daptomycin | Standard of Care (SOC) | Age Group 1: Daptomycin |
|---|---|---|---|
| Number of subjects | 257 | 132 | 73 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous | | | |
| For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available. | | | |
| Units: years<br>arithmetic mean<br>standard deviation | <br>8.25<br>± 5.162 | <br>8.14<br>± 5.098 | <br>15.02<br>± 1.584 |
| Gender categorical | | | |
| Gender was not known for 7 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 126 | 62 | 29 |
| Male | 131 | 70 | 44 |

| **Reporting group values** | Age Group 1: Standard of Care (SOC) | Age Group 2: Daptomycin | Age Group 2: SOC |
|---|---|---|---|
| Number of subjects | 37 | 73 | 38 |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous | | | |
| For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available. | | | |
| Units: years | | | |
| arithmetic mean | 14.84 | 9.05 | 8.98 |
| standard deviation | ± 1.735 | ± 1.443 | ± 1.305 |
| Gender categorical | | | |
| Gender was not known for 7 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 15 | 28 | 15 |
| Male | 22 | 45 | 23 |

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

| | | | |
|---|---|---|---|
| Age continuous | | | |
| For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available. | | | |
| Units: years | | | |
| arithmetic mean | 3.92 | 3.86 | 1.46 |
| standard deviation | ± 1.556 | ± 1.555 | ± 0.231 |
| Gender categorical | | | |
| Gender was not known for 7 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 48 | 20 | 21 |
| Male | 33 | 22 | 9 |

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

| | | | |
|---|---|---|---|
| Age continuous | | | |
| For the overall study period, the mean (SD) is for 389 subjects for whom evaluable data was available. | | | |
| Units: years | | | |
| arithmetic mean | 1.43 | | |
| standard deviation | ± 0.299 | | |
| Gender categorical | | | |
| Gender was not known for 7 subjects in the overall study baseline population. These subjects were counted in the male catagory for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 12 | | |
| Male | 3 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Daptomycin |
| Reporting group description: | |
| Administered intravenously (IV) every 24 hours for up to 14 days at age-dependent dosages. | |
| Reporting group title | Standard of Care (SOC) |
| Reporting group description: | |
| The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. | |
| Subject analysis set title | Daptomycin |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects who received at least 1 dose of study drug. | |
| Subject analysis set title | Standard of Care (SOC) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Subjects who received at least 1 dose of study drug. | |
| Subject analysis set title | Age Group 1: Daptomycin |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Daptomycin: 5 mg/kg administered IV every 24 hours for up to 14 days Age Group 1: Participants ages 12 to 17 years | |
| Subject analysis set title | Age Group 1: Standard of Care (SOC) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days. Age Group 1: Participants ages 12 to 17 years | |
| Subject analysis set title | Age Group 2: Daptomycin |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Daptomycin: 7 mg/kg administered IV every 24 hours for up to 14 days Age Group 2: Participants ages 7 to 11 years | |
| Subject analysis set title | Age Group 2: SOC |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days. Age Group 2: Participants ages 7 to 11 years | |
| Subject analysis set title | Age Group 3: Daptomycin |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Daptomycin: 9 mg/kg administered IV every 24 hours for up to 14 days Age Group 3: Participants ages 2 to 6 years | |
| Subject analysis set title | Age Group 3: SOC |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| SOC: The comparator agent for this study was the SOC treatment and dosage deemed appropriate by the Investigator. The recommended SOC agents were IV vancomycin, IV clindamycin, and IV semisynthetic penicillins every 24 hours for up to 14 days. Age Group 3: Participants ages 2 to 6 years | |
| Subject analysis set title | Age Group 4: Daptomycin |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

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

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

Subject analysis set description:

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

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

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

End point description:

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

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

End point timeframe:

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

Notes:

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

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

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Notes:

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

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

### Statistical analyses

| Statistical analysis title | Percent difference in success rate |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Daptomycin v Standard of Care (SOC) |
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| Parameter estimate | Percent difference |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.7 |
| upper limit | 8.5 |

Notes:

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

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

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

End point description:

Participants who volunteered for PK sampling had a blood sample collected for analysis at the following time points: Age Group 1; Day 3: Predose, 0.25 hour (hr), 1 hr, 4 hr, and12 hr postdose. Age Group 2; Day 3: Predose, 0.25 hr, 1 hr, 6 hr, and 10 hr postdose. Age Group 3; Day 1, 2, or 3: Predose, 0.25 hr, 1 hr, 6 hr, and 8 hr postdose. Age Group 4; Day 1, 2, or 3: 0, 1, 2, 4, and 6 hr relative to end of infusion. Due to limited PK samples, where measures could not be calculated, a "0" is reported. Due to limited PK samples, PK parameters were computed using the mean concentration-time profile during a sampling interval. As a result, no variability could be calculated for data where "0" is reported.

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

End point timeframe:

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

| **End point values** | Age Group 1: Daptomycin | Age Group 2: Daptomycin | Age Group 3: Daptomycin | Age Group 4: Daptomycin |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6[7] | 2[8] | 7[9] | 30[10] |
| Units: microgram*hour per milliliter (µg*hr/mL) | | | | |
| arithmetic mean (standard deviation) | 318 (± 62.2) | 331 (± 23.2) | 318 (± 68.6) | 466 (± 0) |

Notes:

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

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

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

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 11.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Age Group 4: Daptomycin |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Age Group 2: Daptomycin |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Standard of Care |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Age Group 1: Daptomycin |

Reporting group description:

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

| | |
|---|---|
| Reporting group title | Age Group 3: Daptomycin |

Reporting group description:

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

| Serious adverse events | Age Group 4: Daptomycin | Age Group 2: Daptomycin | Standard of Care |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 73 (1.37%) | 3 / 133 (2.26%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 0 / 133 (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 |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| Wound drainage | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 73 (1.37%) | 0 / 133 (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 | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 0 / 133 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 73 (1.37%) | 0 / 133 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Status asthmaticus | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 0 / 133 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Myopathy | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 0 / 133 (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 | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 1 / 73 (1.37%) | 0 / 133 (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 | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 1 / 133 (0.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 0 / 133 (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 |
| Toxic shock syndrome | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 73 (0.00%) | 1 / 133 (0.75%) |
| 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** | Age Group 1: Daptomycin | Age Group 3: Daptomycin | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 72 (4.17%) | 2 / 81 (2.47%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Wound drainage | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 81 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Status asthmaticus | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 1 / 81 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myopathy | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 72 (1.39%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic shock syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 72 (0.00%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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** | Age Group 4: Daptomycin | Age Group 2: Daptomycin | Standard of Care |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 30 (33.33%) | 6 / 73 (8.22%) | 20 / 133 (15.04%) |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 30 (3.33%) | 0 / 73 (0.00%) | 7 / 133 (5.26%) |
| occurrences (all) | 1 | 0 | 7 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 2 / 73 (2.74%) | 3 / 133 (2.26%) |
| occurrences (all) | 0 | 2 | 4 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 4 / 73 (5.48%) | 4 / 133 (3.01%) |
| occurrences (all) | 2 | 4 | 4 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 3 / 73 (4.11%) | 7 / 133 (5.26%) |
| occurrences (all) | 0 | 3 | 7 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 1 / 73 (1.37%) | 1 / 133 (0.75%) |
| occurrences (all) | 3 | 1 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 73 (0.00%) | 1 / 133 (0.75%) |
| occurrences (all) | 2 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis diaper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 73 (0.00%) | 3 / 133 (2.26%) |
| occurrences (all) | 2 | 0 | 3 |
| Rash papular | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 73 (0.00%) | 1 / 133 (0.75%) |
| occurrences (all) | 2 | 0 | 1 |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 73 (0.00%) | 0 / 133 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 73 (0.00%) | 0 / 133 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| **Non-serious adverse events** | Age Group 1: Daptomycin | Age Group 3: Daptomycin | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 72 (18.06%) | 25 / 81 (30.86%) | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 4 / 72 (5.56%) | 8 / 81 (9.88%) | |
| occurrences (all) | 4 | 8 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 72 (6.94%) | 0 / 81 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 72 (2.78%) | 1 / 81 (1.23%) | |
| occurrences (all) | 2 | 1 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 72 (4.17%) | 12 / 81 (14.81%) | |
| occurrences (all) | 3 | 13 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 72 (0.00%) | 4 / 81 (4.94%) | |
| occurrences (all) | 0 | 4 | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|---|---|---|
| disorders<br>Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 72 (0.00%)<br>0 | <br><br>2 / 81 (2.47%)<br>2 | |
| Skin and subcutaneous tissue disorders<br>Dermatitis diaper<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash papular<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 72 (0.00%)<br>0<br><br><br>1 / 72 (1.39%)<br>1 | <br><br>0 / 81 (0.00%)<br>0<br><br><br>0 / 81 (0.00%)<br>0 | |
| Infections and infestations<br>Cellulitis<br>subjects affected / exposed<br>occurrences (all) | <br><br>1 / 72 (1.39%)<br>1 | <br><br>1 / 81 (1.23%)<br>1 | |
| Metabolism and nutrition disorders<br>Hyperphosphataemia<br>subjects affected / exposed<br>occurrences (all) | <br><br>0 / 72 (0.00%)<br>0 | <br><br>1 / 81 (1.23%)<br>1 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported