



Clinical trial results:

An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged 3 Months to Twenty-Four Months Who Are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Bacterial Infection Including Peri-Operative Prophylactic Use of Antibiotics

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002779-64 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 20 March 2012 |

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 | 3009-018 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01019395 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Cubist Pharmaceuticals |
| Sponsor organisation address | 65 Hayden Avenue, Lexington, United States, 02421 |
| Public contact | Study Director, Cubist Pharmaceuticals, +1 781-860-8660, |
| Scientific contact | Study Director, Cubist Pharmaceuticals, +1 781-860-8660, |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 August 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 March 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 March 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate single dose pharmacokinetics (PK) data of intravenous (i.v.) daptomycin administered at 4 milligrams per kilogram (mg/kg) or 6 mg/kg as a 30 minute infusion in pediatric subjects aged 3 to 24 months, inclusive, with proven or suspected bacterial infection who were receiving standard antibiotic therapy, including subjects that were receiving prophylactic antibiotics peri-operatively.

Protection of trial subjects:

This open-label study did not employ any blinding methods. Screening assessments included medical and medication history, demographics, physical examination, vital signs, a brief neurology examination, electrocardiogram, clinical laboratory tests (hematology, chemistry, urinalysis, serum creatine kinase, and serum creatinine). Study subjects were monitored for adverse events. The study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practices (GCP), Food and Drug Administration (FDA) Code of Federal Regulations (CFR) 312.120, and applicable local regulatory requirements. The protocol, informed consent form (ICF), and all other written documents provided to the parent (or appropriate legal representative) were reviewed and approved by an independent Institutional Review Board (IRB) at each site before the study began. In addition, this study enrolled in a stepwise fashion. It began with age group 1 and after review of PK and safety data, age group 2 was enrolled, and continued in this manner.

Background therapy: -

Evidence for comparator:

This was a non-comparative study.

| | |
|---|-----------------|
| Actual start date of recruitment | 13 January 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 32 |
| Worldwide total number of subjects | 32 |
| 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) | 32 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Written parental (or appropriate legal representative) informed consent was obtained prior to the initiation of any of the assessments/procedures required by the protocol, and subjects met all of the inclusion and none of the exclusion criteria prior to enrollment in this study. Eligible subjects received open-label study drug treatment.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Daptomycin 6 mg/kg: Ages 13 months to 24 months |

Arm description:

Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.

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

Dosage and administration details:

All subjects received a single-dose of daptomycin 6 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 30 minutes. The dosing volume was 25 millilitres (mL) and the infusion rate was 0.83 mL per minute for the 30 minute infusion.

| | |
|------------------|--|
| Arm title | Daptomycin 4 mg/kg: Ages 7 months to 12 months |
|------------------|--|

Arm description:

Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

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

Dosage and administration details:

All subjects received a single-dose of daptomycin 4 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 30 minutes. The dosing volume was 25 mL and the infusion rate was 0.83 mL per minute for the 30 minute infusion.

| | |
|------------------|---|
| Arm title | Daptomycin 4 mg/kg: Ages 3 months to 6 months |
|------------------|---|

Arm description:

Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

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

| | |
|--|------------------------|
| Investigational medicinal product name | Daptomycin |
| Investigational medicinal product code | |
| Other name | Cubicin® |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

All subjects received a single-dose of daptomycin 4 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 30 minutes. The dosing volume was 25 mL and the infusion rate was 0.83 mL per minute for the 30 minute infusion.

| Number of subjects in period 1 | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months |
|--|---|--|---|
| Started | 13 | 9 | 10 |
| Subjects that received a complete dose | 7 | 8 | 9 |
| Completed | 7 | 7 | 9 |
| Not completed | 6 | 2 | 1 |
| Not Specified | 4 | 1 | - |
| Parent's Decision | 2 | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Daptomycin 6 mg/kg: Ages 13 months to 24 months |
| Reporting group description: Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes. | |
| Reporting group title | Daptomycin 4 mg/kg: Ages 7 months to 12 months |
| Reporting group description: Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes. | |
| Reporting group title | Daptomycin 4 mg/kg: Ages 3 months to 6 months |
| Reporting group description: Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes. | |

| Reporting group values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months |
|---|---|--|---|
| Number of subjects | 13 | 9 | 10 |
| Age categorical | | | |
| Age of all enrolled subjects and all subjects that received a complete dose of study drug. | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 13 | 9 | 10 |
| Age continuous | | | |
| Age of all subjects that received a complete dose of study drug presented. Age of all enrolled subjects was not calculated and values of "0" were presented. | | | |
| Units: months | | | |
| arithmetic mean | 0 | 0 | 0 |
| standard deviation | ± 0 | ± 0 | ± 0 |
| Gender categorical | | | |
| Gender of all subjects that received a complete dose of study drug is presented. Gender was not known for 8 subjects in the overall study baseline population. These subjects were counted in the male category for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 3 | 4 | 8 |
| Male | 10 | 5 | 2 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 32 | | |
| Age categorical | | | |
| Age of all enrolled subjects and all subjects that received a complete dose of study drug. | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 32 | | |
| Age continuous | | | |
| Age of all subjects that received a complete dose of study drug presented. Age of all enrolled subjects was not calculated and values of "0" were presented. | | | |
| Units: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

| | | | |
|---|----|--|--|
| Gender categorical | | | |
| Gender of all subjects that received a complete dose of study drug is presented. Gender was not known for 8 subjects in the overall study baseline population. These subjects were counted in the male category for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 15 | | |
| Male | 17 | | |

Subject analysis sets

| | |
|----------------------------|--|
| Subject analysis set title | Daptomycin 6 mg/kg: Ages 13 to 24 months - Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.

| | |
|----------------------------|---|
| Subject analysis set title | Daptomycin 4 mg/kg: Ages 7 to 12 months - Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

| | |
|----------------------------|--|
| Subject analysis set title | Daptomycin 4 mg/kg: Ages 3 to 6 months - Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

| Reporting group values | Daptomycin 6 mg/kg: Ages 13 to 24 months - Safety Population | Daptomycin 4 mg/kg: Ages 7 to 12 months - Safety Population | Daptomycin 4 mg/kg: Ages 3 to 6 months - Safety Population |
|---|--|---|--|
| Number of subjects | 7 | 8 | 9 |
| Age categorical | | | |
| Age of all enrolled subjects and all subjects that received a complete dose of study drug. | | | |
| Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 7 | 8 | 9 |
| Age continuous | | | |
| Age of all subjects that received a complete dose of study drug presented. Age of all enrolled subjects was not calculated and values of "0" were presented. | | | |
| Units: months | | | |
| arithmetic mean | 19.46 | 9.8 | 4.79 |
| standard deviation | ± 1.459 | ± 1.708 | ± 1.374 |
| Gender categorical | | | |
| Gender of all subjects that received a complete dose of study drug is presented. Gender was not known for 8 subjects in the overall study baseline population. These subjects were counted in the male category for the overall baseline population. They are not included in the subject analysis populations. | | | |
| Units: Subjects | | | |
| Female | 3 | 4 | 8 |
| Male | 4 | 4 | 1 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Daptomycin 6 mg/kg: Ages 13 months to 24 months |
| Reporting group description: Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes. | |
| Reporting group title | Daptomycin 4 mg/kg: Ages 7 months to 12 months |
| Reporting group description: Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes. | |
| Reporting group title | Daptomycin 4 mg/kg: Ages 3 months to 6 months |
| Reporting group description: Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes. | |
| Subject analysis set title | Daptomycin 6 mg/kg: Ages 13 to 24 months - Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes. | |
| Subject analysis set title | Daptomycin 4 mg/kg: Ages 7 to 12 months - Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes. | |
| Subject analysis set title | Daptomycin 4 mg/kg: Ages 3 to 6 months - Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes. | |

Primary: Pharmacokinetics of daptomycin: Maximum plasma concentration

| | |
|---|---|
| End point title | Pharmacokinetics of daptomycin: Maximum plasma concentration ^[1] |
| End point description: Maximum plasma concentration (C _{max}) presented in micrograms per milliliter over the entire sampling phase directly obtained from the experimental plasma concentration time data, without interpolation. | |
| End point type | Primary |
| End point timeframe: Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion. | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed. | |

| End point values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 | 7 | 7 | |
| Units: micrograms per millilitre | | | | |
| arithmetic mean (standard deviation) | 67 (± 14.5) | 37.1 (± 12.6) | 38.7 (± 5.2) | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Area under the plasma concentration-time curve

| | |
|-----------------|---|
| End point title | Pharmacokinetics of daptomycin: Area under the plasma concentration-time curve ^[2] |
|-----------------|---|

End point description:

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

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

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

| | | | | |
|--|---|--|---|--|
| End point values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | |
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 | 7 | 7 | |
| Units: micrograms times hours per millilitre | | | | |
| arithmetic mean (standard deviation) | 281.5 (± 44.5) | 219.3 (± 66.8) | 215 (± 68.3) | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Time to maximum concentration

| | |
|-----------------|--|
| End point title | Pharmacokinetics of daptomycin: Time to maximum concentration ^[3] |
|-----------------|--|

End point description:

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

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

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

| End point values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 | 7 | 7 | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 0.66 (± 0.26) | 0.59 (± 0.2) | 0.53 (± 0.02) | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Half-life

| | |
|------------------------|--|
| End point title | Pharmacokinetics of daptomycin: Half-life ^[4] |
| End point description: | The apparent elimination half-life (t _{1/2}) of daptomycin presented in hours calculated as natural logarithm of 2 divided by the terminal slope of the concentration versus time curve (Kel). |
| End point type | Primary |
| End point timeframe: | Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion. |

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

| End point values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 | 7 | 7 | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | 4.41 (± 0.94) | 5.45 (± 1.13) | 5.1 (± 1.17) | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Clearance

| | |
|------------------------|--|
| End point title | Pharmacokinetics of daptomycin: Clearance ^[5] |
| End point description: | Plasma clearance (CL) calculated as dose divided by AUC _{0-∞} is presented in millilitres per hour(s) per kilogram. |

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

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

| End point values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | |
|---|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 | 7 | 7 | |
| Units: millilitre(s) per hour(s) per kilogram | | | | |
| arithmetic mean (standard deviation) | 21.76 (± 2.99) | 19.63 (± 5.76) | 19.72 (± 5.46) | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Volume of distribution

| | |
|-----------------|---|
| End point title | Pharmacokinetics of daptomycin: Volume of distribution ^[6] |
|-----------------|---|

End point description:

Steady state weight adjusted volume of distribution (V_{ss}) presented in millilitres per kilogram calculated as a product of CL and mean residence time.

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

End point timeframe:

Pre-dose, at end of infusion, and 1 hours, 2 hours, 6 hours, and 12 hours after the start of infusion.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was a Phase 1, single dose, open-label, non-comparative study and therefore only descriptive analyses were performed. No statistical tests were performed.

| End point values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 5 | 7 | 7 | |
| Units: Millilitre(s) per kilogram | | | | |
| arithmetic mean (standard deviation) | 121.7 (± 30.7) | 134.9 (± 28.6) | 127.7 (± 11.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety of daptomycin: Treatment-emergent related adverse events

| | |
|---|---|
| End point title | Safety of daptomycin: Treatment-emergent related adverse events |
| End point description: The number of subjects with at least one treatment-emergent related adverse event was reported by dosing group. | |
| End point type | Secondary |
| End point timeframe: Up to 9 days after dosing. | |

| End point values | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7 | 8 | 9 | |
| Units: Subjects | 0 | 3 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up through 9 days post-dose.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Daptomycin 6 mg/kg: Ages 13 months to 24 months |
|-----------------------|---|

Reporting group description:

Subjects aged 13 months to 24 months inclusive received a single dose of i.v. daptomycin 6 mg/kg over a duration of 30 minutes.

| | |
|-----------------------|---|
| Reporting group title | Daptomycin 4 mg/kg: Ages 3 months to 6 months |
|-----------------------|---|

Reporting group description:

Subjects aged 3 months to 6 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

| | |
|-----------------------|--|
| Reporting group title | Daptomycin 4 mg/kg: Ages 7 months to 12 months |
|-----------------------|--|

Reporting group description:

Subjects aged 7 months to 12 months inclusive received a single dose of i.v. daptomycin 4 mg/kg over a duration of 30 minutes.

| Serious adverse events | Daptomycin 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months |
|--|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 7 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 6 mg/kg: Ages 13 months to 24 months | Daptomycin 4 mg/kg: Ages 3 months to 6 months | Daptomycin 4 mg/kg: Ages 7 months to 12 months |
|--|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 2 / 7 (28.57%) | 3 / 9 (33.33%) | 6 / 8 (75.00%) |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed | 0 / 7 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Aspartate aminotransferase increased subjects affected / exposed | 0 / 7 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased subjects affected / exposed | 0 / 7 (0.00%) | 0 / 9 (0.00%) | 3 / 8 (37.50%) |
| occurrences (all) | 0 | 0 | 3 |
| Eosinophil count increased subjects affected / exposed | 0 / 7 (0.00%) | 1 / 9 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urine output decreased subjects affected / exposed | 0 / 7 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Hyperreflexia subjects affected / exposed | 0 / 7 (0.00%) | 1 / 9 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertonia subjects affected / exposed | 0 / 7 (0.00%) | 1 / 9 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Irritability subjects affected / exposed | 0 / 7 (0.00%) | 0 / 9 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Pyrexia subjects affected / exposed | 1 / 7 (14.29%) | 0 / 9 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Constipation subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 2 / 9 (22.22%) 2 | 0 / 8 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 9 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Teething subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis diaper subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | 0 / 9 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Rash macular subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 2 |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 2 |
| Skin exfoliation subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Infections and infestations | | | |
| Otitis media subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Metabolism and nutrition disorders | | | |
| Hypophagia subjects affected / exposed occurrences (all) | 0 / 7 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 8 (12.50%) 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 19 November 2009 | <ul style="list-style-type: none">• Dosing for Group 1 (ages 13 months to 24 months) was changed from 9 mg/kg over a 1 hour infusion to 6 mg/kg over a 30 minute infusion. In addition, infusion times were updated for Group 2 (ages 7 months to 12 months) and Group 3 (ages 3 months to 6 months) to include the possibility of a 30 minute infusion.• Enrollment was to begin with Group 1.• Pharmacokinetic sampling time points were adjusted accordingly to account for the revised dosing. |
| 02 September 2010 | <ul style="list-style-type: none">• Based on the review of clinical data from 4 infants in Age Group 1, the dose of study medication was reduced to 4 mg/kg administered over 30 minutes for children younger than 13 months of age (Age Groups 2 and 3). The 6 mg/kg dose, administered over 30 minutes, was continued for Age Group 1. Age Groups 2 and 3 were to be enrolled simultaneously.• An inclusion criterion was added that requires the presence of two patent i.v. lines (or comparable means of venous access) prior to dosing on Study Day 1.• The timing of PK plasma sample collection was revised to reflect the revised infusion schedule. |
| 20 July 2011 | <ul style="list-style-type: none">• The option for a 1 hour or 2 hour infusion was removed since both dose groups received 4 mg/kg which was infused over 30 minutes.• The Baseline evaluation screening window was changed from 48 hour prior to dosing to 2 weeks prior to dosing to allow a larger window for screening.• To account for the difficulty placing 12 leads on the subjects in the youngest age group, the requirement for a 12-lead ECG was changed to an ECG.• Revision of inclusion criterion 5 to state that subjects had to have suspected or diagnosed bacterial infection instead of a gram positive infection. The subject was also to have received standard antibiotic therapy, including prophylactic use of antibiotics peri-operatively.• Revisions of various other inclusion and exclusion criteria.• Concomitant antibiotics and medications and concurrent procedures was revised to account for the inclusion of surgical subjects. The following changes were made: the requirements that surgical procedures could not be performed within 24 hours prior to dosing and that subjects were not to plan procedures in the 24 hours following dosing were deleted.• The number of samples required for PK collection was reduced from 6 to 5, thus eliminating the pre-dose draw. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported