



Clinical trial results:

An Evaluation of the Pharmacokinetic Profile and Safety of a Single Dose of Daptomycin in Pediatric Subjects Aged Two to Six Years Who are Concurrently Receiving Standard Antibiotic Therapy for Proven or Suspected Gram-positive Infection

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-002781-23 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 20 November 2008 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 05 April 2016 |
| First version publication date | 02 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | DAP-PEDS-07-02 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00679835 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Cubist Pharmaceuticals |
| Sponsor organisation address | 65 Hayden Avenue, Lexington, United States, 02421 |
| Public contact | Medical Director, Cubist Pharmaceuticals, +1 781-860-8660 , |
| Scientific contact | Medical 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 | 26 May 2009 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 November 2008 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 November 2008 |
| 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 pharmacokinetic (PK) data on intravenous (i.v.) daptomycin administered at 8 milligrams per kilogram (mg/kg) as a 1 hour infusion or 10 mg/kg as either a 1 or 2 hour infusion in pediatric subjects aged 2 to 6 years, inclusive, with proven or suspected Gram-positive infection who were receiving standard antibiotic therapy.

Protection of trial subjects:

This open-label study did not employ any blinding methods. Screening assessments included demographics and medical history, physical examination, vital signs, brief neurologic examination, electrocardiogram, and clinical laboratory tests (chemistry, hematology, urinalysis, serum creatinine, and serum creatine phosphokinase). Study subjects were monitored for adverse events. After the first 6 subjects enrolled in Group 1 had completed laboratory testing and the follow-up visit, the Investigators and the Sponsor's medical and PK representatives reviewed pertinent PK and safety data and decided whether or not to continue enrollment to 12 subjects.

Background therapy: -

Evidence for comparator:

This was a non-comparative study.

| | |
|---|--------------|
| Actual start date of recruitment | 03 June 2008 |
| 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: 12 |
| Worldwide total number of subjects | 12 |
| 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) | 0 |
| Children (2-11 years) | 12 |

| | |
|---------------------------|---|
| 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 and written subject assent (as appropriate) was obtained, 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 8 mg/kg |

Arm description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

| | |
|--|------------------------|
| 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 8 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 1 hour via a syringe pump. The dosing volume was 25 millilitres (mL) and the infusion rate was 0.42 mL per minute for the 1-hour infusion.

| | |
|------------------|---------------------|
| Arm title | Daptomycin 10 mg/kg |
|------------------|---------------------|

Arm description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

| | |
|--|------------------------|
| 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 10 mg/kg dissolved in 0.9% sodium chloride for injection. Daptomycin was administered i.v. over 1 hour via a syringe pump. The dosing volume was 25 mL and the infusion rate was 0.42 mL per minute for the 1-hour infusion.

| Number of subjects in period 1 | Daptomycin 8 mg/kg | Daptomycin 10 mg/kg |
|--|-----------------------|------------------------|
| Started | 6 | 6 |
| Subjects that received a complete dose | 6 | 6 |
| Completed | 6 | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Daptomycin 8 mg/kg |
|-----------------------|--------------------|

Reporting group description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

| | |
|-----------------------|---------------------|
| Reporting group title | Daptomycin 10 mg/kg |
|-----------------------|---------------------|

Reporting group description:

Subjects received a single dose of daptomycin over a duration of 1 hour.

| Reporting group values | Daptomycin 8 mg/kg | Daptomycin 10 mg/kg | Total |
|---|--------------------|---------------------|-------|
| Number of subjects | 6 | 6 | 12 |
| Age categorical | | | |
| Age of all enrolled subjects by category. | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 6 | 6 | 12 |
| Age continuous | | | |
| Age of all enrolled subjects. | | | |
| Units: years | | | |
| arithmetic mean | 3.85 | 4.43 | |
| standard deviation | ± 1.88 | ± 1.136 | - |
| Gender categorical | | | |
| Gender of all enrolled subjects. | | | |
| Units: Subjects | | | |
| Female | 3 | 2 | 5 |
| Male | 3 | 4 | 7 |

End points

End points reporting groups

| | |
|--|---------------------|
| Reporting group title | Daptomycin 8 mg/kg |
| Reporting group description: Subjects received a single dose of daptomycin over a duration of 1 hour. | |
| Reporting group title | Daptomycin 10 mg/kg |
| Reporting group description: Subjects received a single dose of daptomycin over a duration of 1 hour. | |

Primary: Pharmacokinetics of daptomycin: Apparent elimination half-life

| | |
|---|--|
| End point title | Pharmacokinetics of daptomycin: Apparent elimination half- |
| 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 (K_{el}). | |
| End point type | Primary |
| End point timeframe: Up to 24 hours post dose. | |
| 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 8 mg/kg | Daptomycin 10 mg/kg | | |
|--------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 5.35 (\pm 1.41) | 5.67 (\pm 0.62) | | |

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 ^[2] |
| End point description: Terminal exponential volume of distribution (V_z) presented in millilitres per kilogram based on the terminal phase calculated as the ratio of plasma clearance (CL) and K_{el} . | |
| End point type | Primary |
| End point timeframe: Up to 24 hours post dose. | |
| 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 8 mg/kg | Daptomycin 10 mg/kg | | |
|--------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: millilitre(s) per kilogram | | | | |
| arithmetic mean (standard deviation) | 142.3 (± 12.28) | 154.8 (± 32.98) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Maximum plasma concentration

| | |
|-----------------|---|
| End point title | Pharmacokinetics of daptomycin: Maximum plasma concentration ^[3] |
|-----------------|---|

End point description:

Maximum plasma concentration (C_{max}) presented in micrograms per millilitre over the entire sampling phase directly obtained from the experimental plasma concentration time data, without interpolation.

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

End point timeframe:

Up to 24 hours post dose.

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 8 mg/kg | Daptomycin 10 mg/kg | | |
|--------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: microgram(s) per millilitre | | | | |
| arithmetic mean (standard deviation) | 68.42 (± 9.33) | 79.18 (± 10.17) | | |

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 ^[4] |
|-----------------|--|

End point description:

Time to maximum concentration (T_{max}) presented 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:

Up to 24 hours post dose.

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 8 mg/kg | Daptomycin 10 mg/kg | | |
|--------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 0.86 (± 0.27) | 1.04 (± 0.04) | | |

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 ^[5] |
|-----------------|---|

End point description:

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

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

End point timeframe:

Up to 24 hours post dose.

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 8 mg/kg | Daptomycin 10 mg/kg | | |
|--|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: microgram(s) times hours per millilitre | | | | |
| arithmetic mean (standard deviation) | 429.14 (± 113.01) | 549.7 (± 139.35) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetics of daptomycin: Clearance

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

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:

Up to 24 hours post dose.

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 8 mg/kg | Daptomycin 10 mg/kg | | |
|---|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: millilitre(s) per hour(s) per kilogram | | | | |
| arithmetic mean (standard deviation) | 19.47 (± 5.01) | 19.14 (± 4.51) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety of daptomycin: Treatment-emergent adverse events

| | |
|-----------------|---|
| End point title | Safety of daptomycin: Treatment-emergent adverse events |
|-----------------|---|

End point description:

The number of subjects with at least one treatment-emergent adverse event was reported by dosing group.

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

End point timeframe:

Up to 9 days after dosing.

| End point values | Daptomycin 8 mg/kg | Daptomycin 10 mg/kg | | |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: Subjects | 2 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up through 7 days post-dose.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Daptomycin 10 mg/kg |
|-----------------------|---------------------|

Reporting group description: -

| | |
|-----------------------|--------------------|
| Reporting group title | Daptomycin 8 mg/kg |
|-----------------------|--------------------|

Reporting group description: -

| Serious adverse events | Daptomycin 10 mg/kg | Daptomycin 8 mg/kg | |
|---|---------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Infections and infestations | | | |
| GROIN ABSCESS | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (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 | Daptomycin 10 mg/kg | Daptomycin 8 mg/kg | |
|---|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 2 / 6 (33.33%) | |
| Investigations | | | |
| BODY TEMPERATURE INCREASED | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular disorders | | | |
| PHLEBITIS | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | |
| Nervous system disorders HEADACHE subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | |
| HYPOAESTHESIA subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| General disorders and administration site conditions CATHETER RELATED COMPLICATION subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | |
| IRRITABILITY subjects affected / exposed occurrences (all) | 0 / 6 (0.00%) 0 | 1 / 6 (16.67%) 1 | |
| Ear and labyrinth disorders CERUMEN IMPACTION subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | |
| TONSILLAR HYPERTROPHY subjects affected / exposed occurrences (all) | 2 / 6 (33.33%) 2 | 0 / 6 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders DRY SKIN subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | |
| PRURITUS subjects affected / exposed occurrences (all) | 1 / 6 (16.67%) 1 | 0 / 6 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|---------------|----------------|--|
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | |
| occurrences (all) | 0 | 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