



## Clinical trial results:

### An Open-Label Study to Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Doripenem in Infants (Term and Preterm), Less Than 12 Weeks Chronological Age

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2009-014387-20       |
| Trial protocol           | BE GB Outside EU/EEA |
| Global end of trial date | 30 April 2012        |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 06 July 2016 |
| First version publication date | 22 July 2015 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | DORI-PED-1003 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01381848 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Janssen-Cilag International NV   |
| Sponsor organisation address | Turnhoutseweg 30, Beerse, Belgium,   |
| Public contact               | Janssen-Cilag International NV, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Janssen-Cilag International NV, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000015-PIP01-07 |
| 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 April 2012 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 April 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 the pharmacokinetics (PK) of doripenem after single-dose administration of doripenem to infants (term and preterm), less than (<) 12 weeks chronological age (CA). Safety and tolerability were also assessed.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Subjects' safety was monitored throughout the study by a safety committee composed of the sponsor's medical monitor and at least 1 of the study's principal investigators. The committee reviewed safety information at least once a month or after every subjects enrolled and dosed. Safety was evaluated by examining incidence, severity, relationship to study drug and types of adverse events, changes in clinical laboratory results (hematology and serum biochemistry), physical examination, vital sign measurements and concomitant therapy.

Background therapy:

All medications were allowed except concomitant use of probenecid valproic acid, and imipenem/cilastatin, which have documented or potential interactions with doripenem.

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 19 November 2009 |
| 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 | Belgium: 36       |
| Country: Number of subjects enrolled | United States: 12 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Worldwide total number of subjects   | 52                |
| EEA total number of subjects         | 40                |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 34 |

|  |    |
|--|----|
| Infants and toddlers (28 days-23 months) | 18 |
| 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:

This study was conducted from 19 Nov 2009 to 30 Apr 2012. A total of 52 subjects were assigned to 1 of the 6 age groups, of which 51 (98%) subjects completed the study. One subject was withdrawn from the study due to personal reasons.

### Pre-assignment

Screening details:

In this study subjects were enrolled based on CA and categorized into either a neonate or infant age group. Thirty-two neonatal male and female subjects, and 16 infant male and female subjects, were to be included in the study population to ensure that at least 48 subjects complete all required assessments.

### Period 1

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

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Group 1 |

Arm description:

Neonates <32 weeks gestational age (GA) and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | DORIBAX                          |
| Investigational medicinal product code |                                  |
| Other name                             | DORIPENEM HYDRATE                |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects  $\geq$ 8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group 2 |
|------------------|---------|

Arm description:

Neonates <32 weeks GA and  $\geq$ 14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | DORIBAX                          |
| Investigational medicinal product code |                                  |
| Other name                             | DORIPENEM HYDRATE                |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Subjects <8 weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects  $\geq$ 8 weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group 3 |
|------------------|---------|

**Arm description:**

Neonates  $\geq 32$  weeks to  $\leq 44$  weeks GA and  $< 14$  days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | DORIBAX                          |
| Investigational medicinal product code |                                  |
| Other name                             | DORIPENEM HYDRATE                |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

**Dosage and administration details:**

Subjects  $< 8$  weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects  $\geq 8$  weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group 4 |
|------------------|---------|

**Arm description:**

Neonates  $\geq 32$  weeks to  $\leq 44$  weeks GA and  $\geq 14$  days to  $< 4$  weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | DORIBAX                          |
| Investigational medicinal product code |                                  |
| Other name                             | DORIPENEM HYDRATE                |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

**Dosage and administration details:**

Subjects  $< 8$  weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects  $\geq 8$  weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group 5 |
|------------------|---------|

**Arm description:**

Infants  $< 32$  weeks GA and 4 weeks to  $< 12$  weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | DORIBAX                          |
| Investigational medicinal product code |                                  |
| Other name                             | DORIPENEM HYDRATE                |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

**Dosage and administration details:**

Subjects  $< 8$  weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects  $\geq 8$  weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Group 6 |
|------------------|---------|

**Arm description:**

Infants  $\geq 32$  weeks to  $\leq 44$  weeks GA and 4 weeks to  $< 12$  weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | DORIBAX                          |
| Investigational medicinal product code |                                  |
| Other name                             | DORIPENEM HYDRATE                |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

**Dosage and administration details:**

Subjects  $< 8$  weeks CA received a single 5 mg/kg doripenem 1-hour infusion, and subjects  $\geq 8$  weeks CA received a single 8-mg/kg doripenem 1-hour infusion.

| <b>Number of subjects in period 1</b> | Group 1 | Group 2 | Group 3 |
|---------------------------------------|---------|---------|---------|
| Started                               | 8       | 9       | 9       |
| Completed                             | 8       | 9       | 9       |
| Not completed                         | 0       | 0       | 0       |
| Other                                 | -       | -       | -       |

| <b>Number of subjects in period 1</b> | Group 4 | Group 5 | Group 6 |
|---------------------------------------|---------|---------|---------|
| Started                               | 8       | 7       | 11      |
| Completed                             | 8       | 7       | 10      |
| Not completed                         | 0       | 0       | 1       |
| Other                                 | -       | -       | 1       |

## Baseline characteristics

### Reporting groups

|  |         |
|--|---------|
| Reporting group title  | Group 1 |
| Reporting group description:<br>Neonates <32 weeks gestational age (GA) and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day            |         |
| Reporting group title  | Group 2 |
| Reporting group description:<br>Neonates <32 weeks GA and ≥14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day                  |         |
| Reporting group title  | Group 3 |
| Reporting group description:<br>Neonates ≥32 weeks to ≤44 weeks GA and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day                 |         |
| Reporting group title  | Group 4 |
| Reporting group description:<br>Neonates ≥32 weeks to ≤44 weeks GA and ≥14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day     |         |
| Reporting group title  | Group 5 |
| Reporting group description:<br>Infants <32 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day              |         |
| Reporting group title  | Group 6 |
| Reporting group description:<br>Infants ≥32 weeks to ≤44 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day |         |

| Reporting group values                      | Group 1 | Group 2 | Group 3 |
|---|---------|---------|---------|
| Number of subjects                          | 8       | 9       | 9       |
| Title for AgeCategorical<br>Units: subjects |         |         |         |
| Newborns (0-27 days)                        | 8       | 9       | 9       |
| Infants and toddlers (28 days-23 months)    | 0       | 0       | 0       |
| Children (2-11 years)                       | 0       | 0       | 0       |
| Adolescents (12-17 years)                   | 0       | 0       | 0       |
| Adults (18-64 years)                        | 0       | 0       | 0       |
| From 65 to 84 years                         | 0       | 0       | 0       |
| 85 years and over                           | 0       | 0       | 0       |
| Title for AgeContinuous<br>Units: days      |         |         |         |
| arithmetic mean                             | 3.6     | 19      | 3.7     |
| standard deviation                          | ± 3.34  | ± 3.61  | ± 2.35  |
| Title for Gender<br>Units: subjects         |         |         |         |
| Female                                      | 4       | 3       | 5       |
| Male  | 4       | 6       | 4       |

| Reporting group values                      | Group 4 | Group 5 | Group 6 |
|---|---------|---------|---------|
| Number of subjects                          | 8       | 7       | 11      |
| Title for AgeCategorical<br>Units: subjects |         |         |         |
| Newborns (0-27 days)                        | 8       | 0       | 0       |
| Infants and toddlers (28 days-23 months)    | 0       | 7       | 11      |
| Children (2-11 years)                       | 0       | 0       | 0       |
| Adolescents (12-17 years)                   | 0       | 0       | 0       |
| Adults (18-64 years)                        | 0       | 0       | 0       |
| From 65 to 84 years                         | 0       | 0       | 0       |
| 85 years and over                           | 0       | 0       | 0       |
| Title for AgeContinuous<br>Units: days      |         |         |         |
| arithmetic mean                             | 16.6    | 52      | 43.2    |
| standard deviation                          | ± 2.88  | ± 12.99 | ± 13.6  |
| Title for Gender<br>Units: subjects         |         |         |         |
| Female                                      | 5       | 5       | 6       |
| Male  | 3       | 2       | 5       |

| Reporting group values                      | Total |  |  |
|---|-------|--|--|
| Number of subjects                          | 52    |  |  |
| Title for AgeCategorical<br>Units: subjects |       |  |  |
| Newborns (0-27 days)                        | 34    |  |  |
| Infants and toddlers (28 days-23 months)    | 18    |  |  |
| 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     |  |  |
| Title for AgeContinuous<br>Units: days      |       |  |  |
| arithmetic mean                             |       |  |  |
| standard deviation                          | -     |  |  |
| Title for Gender<br>Units: subjects         |       |  |  |
| Female                                      | 28    |  |  |
| Male  | 24    |  |  |



## End points

### End points reporting groups

|  |         |
|--|---------|
| Reporting group title  | Group 1 |
| Reporting group description:<br>Neonates <32 weeks gestational age (GA) and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day            |         |
| Reporting group title  | Group 2 |
| Reporting group description:<br>Neonates <32 weeks GA and ≥14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day                  |         |
| Reporting group title  | Group 3 |
| Reporting group description:<br>Neonates ≥32 weeks to ≤44 weeks GA and <14 days CA, doripenem 5 mg/kg body weight by 1-hour infusion per day                 |         |
| Reporting group title  | Group 4 |
| Reporting group description:<br>Neonates ≥32 weeks to ≤44 weeks GA and ≥14 days to <4 weeks CA, doripenem 5 mg/kg body weight by 1-hour infusion per day     |         |
| Reporting group title  | Group 5 |
| Reporting group description:<br>Infants <32 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day              |         |
| Reporting group title  | Group 6 |
| Reporting group description:<br>Infants ≥32 weeks to ≤44 weeks GA and 4 weeks to <12 weeks CA, doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day |         |

### Primary: Maximum Observed Plasma Concentration (C<sub>max</sub>) of Doripenem

|   |   |
|---|---|
| End point title   | Maximum Observed Plasma Concentration (C <sub>max</sub> ) of Doripenem <sup>[1]</sup> |
| End point description:<br>PK analysis was conducted in subjects with at least 1 PK blood sample.  |   |
| End point type  | Primary   |
| End point timeframe:<br>Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion   |   |
| Notes:<br>[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.<br>Justification: Statistical data were not planned to be reported. |   |

| End point values                          | Group 1         | Group 2         | Group 3         | Group 4         |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type                        | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed               | 8               | 8               | 8               | 8               |
| Units: microgram per milliliters (mcg/mL) |                 |                 |                 |                 |
| arithmetic mean (standard deviation)      | 12.2 (± 3.67)   | 13.2 (± 2.12)   | 13.7 (± 2.03)   | 9.91 (± 0.723)  |

| End point values                          | Group 5          | Group 6         |  |  |
|---|------------------|-----------------|--|--|
| Subject group type                        | Reporting group  | Reporting group |  |  |
| Number of subjects analysed               | 5 <sup>[2]</sup> | 9               |  |  |
| Units: microgram per milliliters (mcg/mL) |                  |                 |  |  |
| arithmetic mean (standard deviation)      | 10.8 (± 4.83)    | 12.3 (± 3.71)   |  |  |

Notes:

[2] - 'N' signifies number of subjects analysed for this end point.

### Statistical analyses

No statistical analyses for this end point

### Primary: Observed Plasma Concentration at the end of the Doripenem Infusion (C<sub>inf</sub>; may or may not be C<sub>max</sub>)

|                 |  |
|-----------------|--|
| End point title | Observed Plasma Concentration at the end of the Doripenem Infusion (C <sub>inf</sub> ; may or may not be C <sub>max</sub> ) <sup>[3]</sup> |
|-----------------|--|

End point description:

PK analysis was conducted in subjects with at least 1 PK blood sample.

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

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end 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: Statistical data were not planned to be reported.

| End point values                     | Group 1         | Group 2         | Group 3         | Group 4         |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 8               | 8               | 8               | 8               |
| Units: mcg/mL                        |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 11.9 (± 4.11)   | 12.7 (± 2.65)   | 13.7 (± 2.03)   | 9.91 (± 0.723)  |

| End point values                     | Group 5          | Group 6         |  |  |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type                   | Reporting group  | Reporting group |  |  |
| Number of subjects analysed          | 5 <sup>[4]</sup> | 9               |  |  |
| Units: mcg/mL                        |                  |                 |  |  |
| arithmetic mean (standard deviation) | 9.9 (± 5.13)     | 12.3 (± 3.71)   |  |  |

Notes:

[4] - 'N' signifies number of subjects analysed for this end point.

### Statistical analyses

No statistical analyses for this end point

---

**Primary: Time to reach the Maximum Observed Plasma Concentration (tmax)**

---

|                 |   |
|-----------------|---|
| End point title | Time to reach the Maximum Observed Plasma Concentration (tmax) <sup>[5]</sup> |
|-----------------|---|

End point description:

PK analysis was conducted in subjects with at least 1 PK blood sample.

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

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end 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: Statistical data were not planned to be reported.

| End point values              | Group 1         | Group 2         | Group 3         | Group 4         |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type            | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed   | 8               | 8               | 8               | 8               |
| Units: hours (h)              |                 |                 |                 |                 |
| median (full range (min-max)) | 1 (1 to 1.5)    | 1 (1 to 1.5)    | 1 (1 to 1)      | 1 (0.98 to 1)   |

| End point values              | Group 5          | Group 6          |  |  |
|-------------------------------|------------------|------------------|--|--|
| Subject group type            | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed   | 5 <sup>[6]</sup> | 9                |  |  |
| Units: hours (h)              |                  |                  |  |  |
| median (full range (min-max)) | 1 (1 to 1.58)    | 1 (0.98 to 1.07) |  |  |

Notes:

[6] - 'N' signifies number of subjects analysed for this end point.

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Primary: Area under the Plasma Concentration-Time Curve From Time 0 to C Last (AUClast)**

---

|                 |   |
|-----------------|---|
| End point title | Area under the Plasma Concentration-Time Curve From Time 0 to C Last (AUClast) <sup>[7]</sup> |
|-----------------|---|

End point description:

Area under the plasma concentration time curve from zero to the last measured concentration (AUClast). PK population included all evaluable subjects who received at least 1 dose of study medication and had sufficient post-dose blood samples to estimate AUClast.

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

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[7] - 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 data were not planned to be reported.

| End point values                                | Group 1         | Group 2         | Group 3         | Group 4         |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type                              | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed                     | 8               | 8               | 8               | 8               |
| Units: microgram*hour per milliliter (mcg.h/mL) |                 |                 |                 |                 |
| arithmetic mean (standard deviation)            | 37.2 (± 5.93)   | 42 (± 7.72)     | 39.4 (± 6.39)   | 24.6 (± 3.77)   |

| End point values                                | Group 5         | Group 6          |  |  |
|---|-----------------|------------------|--|--|
| Subject group type                              | Reporting group | Reporting group  |  |  |
| Number of subjects analysed                     | 6               | 8 <sup>[8]</sup> |  |  |
| Units: microgram*hour per milliliter (mcg.h/mL) |                 |                  |  |  |
| arithmetic mean (standard deviation)            | 35 (± 14.8)     | 30 (± 6.91)      |  |  |

Notes:

[8] - 'N' signifies number of subjects analysed for this end point.

### Statistical analyses

No statistical analyses for this end point

### Primary: Area Under the Plasma Concentration-Time Curve From Time 0 to Infinite Time (AUC [0 - infinity])

|                 |   |
|-----------------|---|
| End point title | Area Under the Plasma Concentration-Time Curve From Time 0 to Infinite Time (AUC [0 - infinity]) <sup>[9]</sup> |
|-----------------|---|

End point description:

AUC (0 - infinity) is area under the plasma concentration versus time curve (AUC) from time zero (predose) to extrapolated infinite time (0 - infinity). PK analysis was conducted in subjects with at least 1 PK blood sample.

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

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[9] - 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 data were not planned to be reported.

| End point values                     | Group 1           | Group 2           | Group 3         | Group 4         |
|--------------------------------------|-------------------|-------------------|-----------------|-----------------|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group | Reporting group |
| Number of subjects analysed          | 7 <sup>[10]</sup> | 7 <sup>[11]</sup> | 8               | 8               |
| Units: mcg.h/mL                      |                   |                   |                 |                 |
| arithmetic mean (standard deviation) | 55.3 (± 10.1)     | 54.6 (± 11.7)     | 49.2 (± 10.9)   | 26.2 (± 4.62)   |

Notes:

[10] - 'N' signifies number of subjects analysed for this end point.

[11] - 'N' signifies number of subjects analysed for this end point.

| End point values            | Group 5           | Group 6           |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 4 <sup>[12]</sup> | 8 <sup>[13]</sup> |  |  |
| Units: mcg.h/mL             |                   |                   |  |  |

|                                      |               |              |  |  |
|--------------------------------------|---------------|--------------|--|--|
| arithmetic mean (standard deviation) | 32.9 (± 15.1) | 32.2 (± 6.8) |  |  |
|--------------------------------------|---------------|--------------|--|--|

Notes:

[12] - 'N' signifies number of subjects analysed for this end point.

[13] - 'N' signifies number of subjects analysed for this end point.

## Statistical analyses

No statistical analyses for this end point

### Primary: Elimination Half-Life (t<sub>1/2</sub>)

|                 |   |
|-----------------|---|
| End point title | Elimination Half-Life (t <sub>1/2</sub> ) <sup>[14]</sup> |
|-----------------|---|

End point description:

Plasma decay half-life is the time measured for the plasma concentration to decrease by one half, associated with the terminal slope (lamda- z) of the semi logarithmic drug concentration-time curve, calculated as 0.693/lamda-z. PK analysis was conducted in subjects with at least 1 PK blood sample.

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

End point timeframe:

Immediately before end of infusion;1.5, 3, 7 hours after end of infusion

Notes:

[14] - 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 data were not planned to be reported.

| End point values                     | Group 1           | Group 2           | Group 3         | Group 4         |
|--------------------------------------|-------------------|-------------------|-----------------|-----------------|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group | Reporting group |
| Number of subjects analysed          | 7 <sup>[15]</sup> | 7 <sup>[16]</sup> | 8               | 8               |
| Units: hours (h)                     |                   |                   |                 |                 |
| arithmetic mean (standard deviation) | 4.22 (± 0.429)    | 3.4 (± 0.894)     | 2.85 (± 0.641)  | 1.66 (± 0.385)  |

Notes:

[15] - 'N' signifies number of subjects analysed for this end point.

[16] - 'N' signifies number of subjects analysed for this end point.

| End point values                     | Group 5           | Group 6           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 4 <sup>[17]</sup> | 8 <sup>[18]</sup> |  |  |
| Units: hours (h)                     |                   |                   |  |  |
| arithmetic mean (standard deviation) | 2.03 (± 0.369)    | 1.67 (± 0.644)    |  |  |

Notes:

[17] - 'N' signifies number of subjects analysed for this end point.

[18] - 'N' signifies number of subjects analysed for this end point.

## Statistical analyses

No statistical analyses for this end point

### Primary: Total Clearance of Drug Normalized by Body Weight (CL/BW)

|                 |   |
|-----------------|---|
| End point title | Total Clearance of Drug Normalized by Body Weight |
|-----------------|---|

End point description:

Total clearance of drug after intravenous administration, calculated as: dose/AUC(0-infinity) (for doripenem only). PK analysis was conducted in subjects with at least 1 PK blood sample.

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

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[19] - 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 data were not planned to be reported.

| End point values                     | Group 1           | Group 2           | Group 3         | Group 4         |
|--------------------------------------|-------------------|-------------------|-----------------|-----------------|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group | Reporting group |
| Number of subjects analysed          | 7 <sup>[20]</sup> | 7 <sup>[21]</sup> | 8               | 8               |
| Units: mL/min/kg                     |                   |                   |                 |                 |
| arithmetic mean (standard deviation) | 1.56 (± 0.34)     | 1.59 (± 0.37)     | 1.78 (± 0.434)  | 3.27 (± 0.589)  |

Notes:

[20] - 'N' signifies number of subjects analysed for this end point.

[21] - 'N' signifies number of subjects analysed for this end point.

| End point values                     | Group 5           | Group 6           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 4 <sup>[22]</sup> | 8 <sup>[23]</sup> |  |  |
| Units: mL/min/kg                     |                   |                   |  |  |
| arithmetic mean (standard deviation) | 3.07 (± 0.474)    | 3.01 (± 0.476)    |  |  |

Notes:

[22] - 'N' signifies number of subjects analysed for this end point.

[23] - 'N' signifies number of subjects analysed for this end point.

## Statistical analyses

No statistical analyses for this end point

## Primary: Apparent Volume of Distribution Normalized by Body Weight (Vdz)/BW

|                 |  |
|-----------------|--|
| End point title | Apparent Volume of Distribution Normalized by Body Weight (Vdz)/BW <sup>[24]</sup> |
|-----------------|--|

End point description:

Apparent volume of distribution based on the terminal phase, calculated as  $D/(\lambda - z \text{ AUC}(0-\infty))$  (for doripenem only). PK analysis was conducted in subjects with at least 1 PK blood sample.

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

End point timeframe:

Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion

Notes:

[24] - 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 data were not planned to be reported.

| End point values                     | Group 1           | Group 2           | Group 3          | Group 4          |
|--------------------------------------|-------------------|-------------------|------------------|------------------|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group  | Reporting group  |
| Number of subjects analysed          | 7 <sup>[25]</sup> | 7 <sup>[26]</sup> | 8                | 8                |
| Units: liters per kilogram (L/kg)    |                   |                   |                  |                  |
| arithmetic mean (standard deviation) | 0.564 (± 0.0975)  | 0.455 (± 0.0859)  | 0.424 (± 0.0597) | 0.461 (± 0.0907) |

Notes:

[25] - 'N' signifies number of subjects analysed for this end point.

[26] - 'N' signifies number of subjects analysed for this end point.

| End point values                     | Group 5           | Group 6           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 4 <sup>[27]</sup> | 8 <sup>[28]</sup> |  |  |
| Units: liters per kilogram (L/kg)    |                   |                   |  |  |
| arithmetic mean (standard deviation) | 0.548 (± 0.151)   | 0.422 (± 0.125)   |  |  |

Notes:

[27] - 'N' signifies number of subjects analysed for this end point.

[28] - 'N' signifies number of subjects analysed for this end point.

## Statistical analyses

No statistical analyses for this end point

## Primary: Creatinine Clearance (CrCL)

|   |   |
|---|---|
| End point title   | Creatinine Clearance (CrCL) <sup>[29]</sup> |
| End point description:<br>For all subjects, using the Schwartz equation, creatinine (cr) clearance (CrCL) was calculated: $k \times \text{length}(\text{cm}) / \text{Cr}$ , where k is a rate constant equal to 0.45 and length (cm) is infact length at the 50th percentile for a subject and Cr is the subjects creatinine concentration in mg/dL. PK analysis was conducted in subjects with at least 1 PK blood sample. |   |
| End point type  | Primary                                     |
| End point timeframe:<br>Immediately before end of infusion; 1.5, 3, 7 hours after end of infusion   |   |

Notes:

[29] - 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 data were not planned to be reported.

| End point values                     | Group 1         | Group 2           | Group 3         | Group 4         |
|--------------------------------------|-----------------|-------------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group   | Reporting group | Reporting group |
| Number of subjects analysed          | 8               | 7 <sup>[30]</sup> | 8               | 8               |
| Units: mL/min/kg                     |                 |                   |                 |                 |
| arithmetic mean (standard deviation) |                 |                   |                 |                 |
| Baseline                             | 18.8 (± 4.98)   | 28.5 (± 7.27)     | 15.1 (± 5.49)   | 24.2 (± 6.44)   |
| End of study                         | 17.8 (± 4.89)   | 30.3 (± 6.8)      | 16.1 (± 6.07)   | 24.7 (± 5.66)   |

Notes:

[30] - 'N' signifies number of subjects analysed for this end point.

| End point values                     | Group 5         | Group 6           |  |  |
|--------------------------------------|-----------------|-------------------|--|--|
| Subject group type                   | Reporting group | Reporting group   |  |  |
| Number of subjects analysed          | 6               | 7 <sup>[31]</sup> |  |  |
| Units: mL/min/kg                     |                 |                   |  |  |
| arithmetic mean (standard deviation) |                 |                   |  |  |
| Baseline                             | 29.7 (± 7.74)   | 18.4 (± 4.71)     |  |  |
| End of study                         | 31.2 (± 10.1)   | 22.2 (± 6.15)     |  |  |

Notes:

[31] - 'N' signifies number of subjects analysed for this end point.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs) |
|-----------------|--|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A Treatment-Emergent Adverse Event (TEAE) is defined as an AE that was new in onset or aggravated in severity or frequency following the start of administration of the study drug and up to Day 7 that were absent before treatment or that worsened relative to pre-treatment state. Safety population included all subjects who received at least one dose of study medication.

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

End point timeframe:

Baseline Up to day 7

| End point values            | Group 1         | Group 2         | Group 3         | Group 4         |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8               | 9               | 9               | 8               |
| Units: subjects             | 3               | 7               | 1               | 3               |

| End point values            | Group 5         | Group 6         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 7               | 11              |  |  |
| Units: subjects             | 4               | 3               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Reporting Treatment-Emergent Serious Adverse Events (TESAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects Reporting Treatment-Emergent Serious Adverse Events (TESAEs) |
|-----------------|---|

End point description:

A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed



significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all subjects who received at least one dose of study medication.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline Up to day 7 |           |

| End point values            | Group 1         | Group 2         | Group 3         | Group 4         |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8               | 9               | 9               | 8               |
| Units: subjects             | 0               | 0               | 0               | 0               |

| End point values            | Group 5         | Group 6         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 7               | 11              |  |  |
| Units: subjects             | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Hematology and Biochemistry Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs)

|  |   |
|--|---|
| End point title  | Number of Subjects With Hematology and Biochemistry Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs) |
| End point description:   |   |
| Hematology profile included hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count and biochemistry profile included sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN) creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, lactic acid dehydrogenase, albumin, total bilirubin, and alkaline phosphatase. Subjects with abnormal hematology and biochemistry parameters recorded as TEAEs were reported. Safety population included all subjects who received at least one dose of study medication. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline up to Day 7   |   |

| End point values            | Group 1         | Group 2         | Group 3         | Group 4         |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8               | 9               | 9               | 8               |
| Units: subjects             |                 |                 |                 |                 |
| Anaemia neonatal            | 0               | 3               | 0               | 0               |
| Leukocytosis                | 0               | 0               | 0               | 0               |
| Hypoalbuminaemia            | 0               | 3               | 0               | 0               |
| Hyperglycaemia              | 1               | 1               | 0               | 0               |
| Hypokalaemia                | 0               | 0               | 0               | 1               |
| Hyponatraemia               | 0               | 1               | 0               | 0               |

| End point values            | Group 5         | Group 6         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 7               | 11              |  |  |
| Units: subjects             |                 |                 |  |  |
| Anaemia neonatal            | 1               | 0               |  |  |
| Leukocytosis                | 0               | 1               |  |  |
| Hypoalbuminaemia            | 0               | 0               |  |  |
| Hyperglycaemia              | 0               | 0               |  |  |
| Hypokalaemia                | 0               | 0               |  |  |
| Hyponatraemia               | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Physical Examination Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs)

|  |  |
|--|--|
| End point title  | Number of Subjects With Physical Examination Abnormalities Recorded as Treatment-Emergent Adverse Events (TEAEs) |
| End point description:<br>Physical examinations were conducted at screening and at the end of the study. Body weight was measured only at screening. Safety population included all subjects who received at least one dose of study medication. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline up to Day 7   |  |

| End point values            | Group 1         | Group 2         | Group 3         | Group 4         |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8               | 9               | 9               | 8               |
| Units: subjects             | 0               | 0               | 0               | 0               |

| End point values            | Group 5         | Group 6         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 7               | 11              |  |  |
| Units: subjects             | 0               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects With Abnormal Vital Signs Recorded as Treatment-Emergent Adverse Events (TEAEs)

|                 |  |
|-----------------|--|
| End point title | Number of subjects With Abnormal Vital Signs Recorded as Treatment-Emergent Adverse Events (TEAEs) |
|-----------------|--|

End point description:

Vital sign assessment included blood pressure, radial pulse rate, body temperature (skin probe, rectal, axillary, or other), and respiration rate. Subjects with abnormal vital signs recorded as TEAEs were reported. Safety population included all subjects who received at least one dose of study medication.

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

End point timeframe:

Baseline up to Day 7

| End point values            | Group 1         | Group 2         | Group 3         | Group 4         |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8               | 9               | 9               | 8               |
| Units: subjects             | 0               | 0               | 0               | 0               |

| End point values            | Group 5         | Group 6         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 7               | 11              |  |  |
| Units: subjects             | 0               | 0               |  |  |

### Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 7

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 15 |
|--------------------|----|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Group 1 |
|-----------------------|---------|

Reporting group description:

Neonates <32 weeks GA and <14 days CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day

|                       |         |
|-----------------------|---------|
| Reporting group title | Group 2 |
|-----------------------|---------|

Reporting group description:

Neonates <32 weeks GA and ≥14 days to <4 weeks CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day

|                       |         |
|-----------------------|---------|
| Reporting group title | Group 3 |
|-----------------------|---------|

Reporting group description:

Neonates ≥32 weeks to ≤44 weeks GA and <14 days CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day

|                       |         |
|-----------------------|---------|
| Reporting group title | Group 4 |
|-----------------------|---------|

Reporting group description:

Neonates ≥32 weeks to ≤44 weeks GA and ≥14 days to <4 weeks CA, Doripenem 5 mg/kg body weight by 1-hour infusion per day

|                       |         |
|-----------------------|---------|
| Reporting group title | Group 5 |
|-----------------------|---------|

Reporting group description:

Infants <32 weeks GA and 4 weeks to <12 weeks CA, Doripenem 5 or 8 mg/kg of body weight by 1-hour infusion per day

|                       |         |
|-----------------------|---------|
| Reporting group title | Group 6 |
|-----------------------|---------|

Reporting group description:

Infants ≥32 weeks to ≤44 weeks GA and 4 weeks to <12 weeks CA, Doripenem 5 or 8 mg/kg body weight by 1-hour infusion per day

| Serious adverse events                            | Group 1       | Group 2       | Group 3       |
|---|---------------|---------------|---------------|
| Total subjects affected by serious adverse events |               |               |               |
| subjects affected / exposed                       | 0 / 8 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (0.00%) |
| number of deaths (all causes)                     | 0             | 0             | 0             |
| number of deaths resulting from adverse events    |               |               |               |
| Infections and infestations                       |               |               |               |
| Sepsis  |               |               |               |
| alternative assessment type: Systematic           |               |               |               |
| subjects affected / exposed                       | 0 / 8 (0.00%) | 0 / 9 (0.00%) | 0 / 9 (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         |

| <b>Serious adverse events</b>                     | Group 4       | Group 5        | Group 6        |
|---|---------------|----------------|----------------|
| Total subjects affected by serious adverse events |               |                |                |
| subjects affected / exposed                       | 0 / 8 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| number of deaths (all causes)                     | 0             | 0              | 0              |
| number of deaths resulting from adverse events    |               |                |                |
| Infections and infestations                       |               |                |                |
| Sepsis  |               |                |                |
| alternative assessment type: Systematic           |               |                |                |
| subjects affected / exposed                       | 0 / 8 (0.00%) | 1 / 7 (14.29%) | 0 / 11 (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          |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Group 1        | Group 2        | Group 3        |
|---|----------------|----------------|----------------|
| Total subjects affected by non-serious adverse events |                |                |                |
| subjects affected / exposed                           | 3 / 8 (37.50%) | 7 / 9 (77.78%) | 1 / 9 (11.11%) |
| Pregnancy, puerperium and perinatal conditions        |                |                |                |
| Umbilical Granuloma                                   |                |                |                |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 0 / 9 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)                                     | 0              | 0              | 0              |
| General disorders and administration site conditions  |                |                |                |
| Drug Tolerance  |                |                |                |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 0 / 9 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)                                     | 0              | 0              | 0              |
| Infusion Site Haematoma                               |                |                |                |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 0 / 9 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)                                     | 0              | 0              | 0              |
| Medical Device Complication                           |                |                |                |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 0 / 9 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)                                     | 0              | 0              | 0              |
| Oedema Peripheral                                     |                |                |                |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 1 / 9 (11.11%) | 0 / 9 (0.00%)  |
| occurrences (all)                                     | 0              | 1              | 0              |
| Respiratory, thoracic and mediastinal disorders       |                |                |                |

|  |  |   |  |
|--|--|---|--|
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0                           | 1 / 9 (11.11%)<br>1                           | 0 / 9 (0.00%)<br>0                           |
| Nasal Congestion<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0                           | 0 / 9 (0.00%)<br>0                            | 1 / 9 (11.11%)<br>1                          |
| Psychiatric disorders<br>Agitation Neonatal<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0                           | 0 / 9 (0.00%)<br>0                            | 0 / 9 (0.00%)<br>0                           |
| Investigations<br>Cardiac Murmur<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0                           | 0 / 9 (0.00%)<br>0                            | 0 / 9 (0.00%)<br>0                           |
| Injury, poisoning and procedural<br>complications<br>Post Procedural Oedema<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0                           | 0 / 9 (0.00%)<br>0                            | 0 / 9 (0.00%)<br>0                           |
| Congenital, familial and genetic<br>disorders<br>Patent Ductus Arteriosus<br>subjects affected / exposed<br>occurrences (all)  | 2 / 8 (25.00%)<br>2                          | 0 / 9 (0.00%)<br>0                            | 0 / 9 (0.00%)<br>0                           |
| Blood and lymphatic system disorders<br>Anaemia Neonatal<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukocytosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0 | 3 / 9 (33.33%)<br>3<br><br>0 / 9 (0.00%)<br>0 | 0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Gastritis Haemorrhagic<br>subjects affected / exposed<br>occurrences (all)<br><br>Ileus Paralytic  | 0 / 8 (0.00%)<br>0<br><br>                   | 1 / 9 (11.11%)<br>1<br><br>                   | 0 / 9 (0.00%)<br>0<br><br>                   |

|   |                     |                     |                    |
|---|---------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 9 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Rash Erythematous<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0 |
| Dermatitis Diaper<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0 |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 8 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 9 (0.00%)<br>0 |
| Infections and infestations<br>Fungal Infection<br>subjects affected / exposed<br>occurrences (all)             | 0 / 8 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 0 / 9 (0.00%)<br>0 |
| Nosocomial Infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1 | 1 / 9 (11.11%)<br>1 | 0 / 9 (0.00%)<br>0 |
| Oral Candidiasis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0 |
| Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 8 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Food Intolerance<br>subjects affected / exposed<br>occurrences (all)      | 0 / 8 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 8 (12.50%)<br>1 | 1 / 9 (11.11%)<br>1 | 0 / 9 (0.00%)<br>0 |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0  | 3 / 9 (33.33%)<br>3 | 0 / 9 (0.00%)<br>0 |
| Hypokalaemia  |                     |                     |                    |



|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 9 (0.00%)  | 0 / 9 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Hyponatraemia               |               |                |               |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 9 (11.11%) | 0 / 9 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |

| <b>Non-serious adverse events</b>                     | Group 4        | Group 5        | Group 6         |
|---|----------------|----------------|-----------------|
| Total subjects affected by non-serious adverse events |                |                |                 |
| subjects affected / exposed                           | 3 / 8 (37.50%) | 3 / 7 (42.86%) | 3 / 11 (27.27%) |
| Pregnancy, puerperium and perinatal conditions        |                |                |                 |
| Umbilical Granuloma                                   |                |                |                 |
| subjects affected / exposed                           | 1 / 8 (12.50%) | 0 / 7 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                                     | 1              | 0              | 0               |
| General disorders and administration site conditions  |                |                |                 |
| Drug Tolerance  |                |                |                 |
| subjects affected / exposed                           | 1 / 8 (12.50%) | 0 / 7 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                                     | 1              | 0              | 0               |
| Infusion Site Haematoma                               |                |                |                 |
| subjects affected / exposed                           | 1 / 8 (12.50%) | 0 / 7 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                                     | 1              | 0              | 0               |
| Medical Device Complication                           |                |                |                 |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 1 / 7 (14.29%) | 0 / 11 (0.00%)  |
| occurrences (all)                                     | 0              | 1              | 0               |
| Oedema Peripheral                                     |                |                |                 |
| subjects affected / exposed                           | 1 / 8 (12.50%) | 0 / 7 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                                     | 1              | 0              | 0               |
| Respiratory, thoracic and mediastinal disorders       |                |                |                 |
| Bronchospasm  |                |                |                 |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 0 / 7 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                                     | 0              | 0              | 0               |
| Nasal Congestion                                      |                |                |                 |
| subjects affected / exposed                           | 0 / 8 (0.00%)  | 0 / 7 (0.00%)  | 0 / 11 (0.00%)  |
| occurrences (all)                                     | 0              | 0              | 0               |
| Psychiatric disorders                                 |                |                |                 |
| Agitation Neonatal                                    |                |                |                 |

|  |  |   |  |
|--|--|---|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0                           | 0 / 7 (0.00%)<br>0                            | 1 / 11 (9.09%)<br>1                            |
| Investigations<br>Cardiac Murmur<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0                           | 0 / 7 (0.00%)<br>0                            | 1 / 11 (9.09%)<br>1                            |
| Injury, poisoning and procedural complications<br>Post Procedural Oedema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0                           | 1 / 7 (14.29%)<br>1                           | 0 / 11 (0.00%)<br>0                            |
| Congenital, familial and genetic disorders<br>Patent Ductus Arteriosus<br>subjects affected / exposed<br>occurrences (all)   | 0 / 8 (0.00%)<br>0                           | 0 / 7 (0.00%)<br>0                            | 0 / 11 (0.00%)<br>0                            |
| Blood and lymphatic system disorders<br>Anaemia Neonatal<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukocytosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1<br><br>0 / 7 (0.00%)<br>0 | 0 / 11 (0.00%)<br>0<br><br>1 / 11 (9.09%)<br>1 |
| Gastrointestinal disorders<br>Gastritis Haemorrhagic<br>subjects affected / exposed<br>occurrences (all)<br><br>Ileus Paralytic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0<br><br>0 / 7 (0.00%)<br>0  | 0 / 11 (0.00%)<br>0<br><br>0 / 11 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Rash Erythematous<br>subjects affected / exposed<br>occurrences (all)<br><br>Dermatitis Diaper<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 8 (0.00%)<br>0<br><br>0 / 8 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0<br><br>1 / 7 (14.29%)<br>1 | 1 / 11 (9.09%)<br>1<br><br>1 / 11 (9.09%)<br>1 |

|                                    |                |                |                |
|------------------------------------|----------------|----------------|----------------|
| Endocrine disorders                |                |                |                |
| Hypothyroidism                     |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Infections and infestations        |                |                |                |
| Fungal Infection                   |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 1              | 0              |
| Nosocomial Infection               |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Oral Candidiasis                   |                |                |                |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 1              | 0              | 0              |
| Respiratory Tract Infection        |                |                |                |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 1              | 0              | 0              |
| Metabolism and nutrition disorders |                |                |                |
| Food Intolerance                   |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 1 / 7 (14.29%) | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 1              | 0              |
| Hyperglycaemia                     |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Hypoalbuminaemia                   |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |
| Hypokalaemia                       |                |                |                |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 1              | 0              | 0              |
| Hyponatraemia                      |                |                |                |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 7 (0.00%)  | 0 / 11 (0.00%) |
| occurrences (all)                  | 0              | 0              | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|  |
|--|
| Sample sizes in all cohorts were relatively small ( $n < 12$ ) limiting the ability to draw definitive conclusions in the safety profile of single 5 or 8 mg/kg doses in neonates and infants $< 12$ weeks CA. |
|--|

Notes: