# Clinical trial results:
# A Multicenter, Double-Blind, Randomized, Comparator-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus Amphotericin B Deoxycholate in the Treatment of Invasive Candidiasis in Neonates and Infants Less Than 3 Months of Age

## Summary

| | |
|---|---|
| EudraCT number | 2013-002084-26 |
| Trial protocol | BG Outside EU/EEA |
| Global end of trial date | 28 February 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 August 2018 |
| First version publication date | 15 August 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 0991-064 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01945281 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 28 February 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

This study evaluated the safety, tolerability, and efficacy of caspofungin as compared with amphotericin B deoxycholate in the treatment of invasive candidiasis in neonates and infants. The primary hypothesis to be tested in the study is that caspofungin was superior to amphotericin B deoxycholate with regard to the proportion of participants with fungal-free survival at the 2-week post-therapy follow-up visit.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 15 January 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Brazil: 5 |
| Country: Number of subjects enrolled | Colombia: 6 |
| Country: Number of subjects enrolled | Mexico: 9 |
| Country: Number of subjects enrolled | South Africa: 17 |
| Country: Number of subjects enrolled | Turkey: 14 |
| Worldwide total number of subjects | 51 |
| 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) | 28 |
| Infants and toddlers (28 days-23 months) | 23 |
| Children (2-11 years) | 0 |

| | |
|---|---|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants less than 3 months of age with invasive candidiasis were enrolled in this study.

### Period 1

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

### Arms

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

Arm description:

Caspofungin 2 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment

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

Dosage and administration details:

Intravenous once daily for ≥14 days

| | |
|---|---|
| **Arm title** | Amphotericin B Deoxycholate |

Arm description:

Amphotericin B deoxycholate 1 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Amphotericin B Deoxycholate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Intravenous once daily for ≥14 days

| **Number of subjects in period 1** | Caspofungin | Amphotericin B Deoxycholate |
|---|---|---|
| Started | 34 | 17 |
| Treated | 33 | 16 |
| Completed | 28 | 13 |
| Not completed | 6 | 4 |
| Adverse event, serious fatal | 3 | 3 |
| Physician decision | 1 | 1 |
| Adverse event, non-fatal | 1 | - |
| Technical Problems | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Caspofungin |
| Reporting group description: | |
| Caspofungin 2 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |
| Reporting group title | Amphotericin B Deoxycholate |
| Reporting group description: | |
| Amphotericin B deoxycholate 1 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |

| Reporting group values | Caspofungin | Amphotericin B Deoxycholate | Total |
|---|---|---|---|
| Number of subjects | 34 | 17 | 51 |
| Age Categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 19 | 9 | 28 |
| Infants and toddlers (28 days-23 months) | 15 | 8 | 23 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: days | | | |
| arithmetic mean | 31.1 | 32.8 | |
| standard deviation | ± 20.9 | ± 23.3 | - |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 14 | 10 | 24 |
| Male | 20 | 7 | 27 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 3 | 1 | 4 |
| Black or African American | 13 | 6 | 19 |
| White | 13 | 8 | 21 |
| More than one race | 5 | 2 | 7 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 12 | 7 | 19 |
| Not Hispanic or Latino | 19 | 9 | 28 |
| Unknown or Not Reported | 3 | 1 | 4 |
| Weight | | | |
| Weight at Baseline Measurement. The population analyzed was participants who received at least 1 full dose of study therapy and had a documented (culture-confirmed) diagnosis of invasive candidiasis. | | | |

| | | | |
|---|---|---|---|
| Units: Grams | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | - |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | Caspofungin |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Caspofungin 2 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment

| | |
|---|---|
| Subject analysis set title | Amphotericin B Deoxycholate |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Amphotericin B deoxycholate 1 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment

| **Reporting group values** | Caspofungin | Amphotericin B Deoxycholate | |
|---|---|---|---|
| Number of subjects | 31 | 16 | |
| Age Categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age Continuous<br>Units: days<br>arithmetic mean<br>standard deviation | ± | ± | |
| Gender Categorical<br>Units: Subjects | | | |
| Female<br>Male | | | |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native<br>Black or African American<br>White<br>More than one race | | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino<br>Not Hispanic or Latino<br>Unknown or Not Reported | | | |

| Weight | | | |
|---|---|---|---|
| Weight at Baseline Measurement. The population analyzed was participants who received at least 1 full dose of study therapy and had a documented (culture-confirmed) diagnosis of invasive candidiasis. | | | |
| Units: Grams | | | |
| arithmetic mean | 1982.1 | 2160.9 | |
| standard deviation | ± 980.6 | ± 1513.8 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Caspofungin |
| Reporting group description: | |
| Caspofungin 2 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |
| Reporting group title | Amphotericin B Deoxycholate |
| Reporting group description: | |
| Amphotericin B deoxycholate 1 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |
| Subject analysis set title | Caspofungin |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Caspofungin 2 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |
| Subject analysis set title | Amphotericin B Deoxycholate |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Amphotericin B deoxycholate 1 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |

### Primary: Percentage of Participants with Fungal-free Survival Through the 2-week Post-therapy Period

| | |
|---|---|
| End point title | Percentage of Participants with Fungal-free Survival Through the 2-week Post-therapy Period |
| End point description: | |
| Fungal-free survival is those participants who survived up to 2 weeks post-therapy, and had documented microbiological eradication of Candida species (sp.) from follow-up cultures collected after the initiation of study therapy. Microbiological eradication denotes negative follow-up cultures for Candida sp. from the site of infection. If a culture is not obtained on the day of assessment, the last culture after study entry may be used to assist in the assessment of microbiological eradication. If the last culture is negative for Candida sp., then microbiological eradication would be considered achieved. The population analyzed was participants who received at least 1 full dose of study therapy and had a documented (culture-confirmed) diagnosis of invasive candidiasis. | |
| End point type | Primary |
| End point timeframe: | |
| Up to 104 days | |

| End point values | Caspofungin | Amphotericin B Deoxycholate | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 16 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 71.0 (52.0 to 85.8) | 68.8 (41.3 to 89.0) | | |

## Statistical analyses

| Statistical analysis title | Caspofungin minus Amphotericin |
|---|---|

Statistical analysis description:

Miettinen & Nurminen method stratified by stratum (Weight category based on weight at study entry) with Cochran Mantel- Haenszel's weights.

| | |
|---|---|
| Comparison groups | Caspofungin v Amphotericin B Deoxycholate |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.3 |
| upper limit | 27.7 |

## Secondary: Percentage of Participants with Fungal-free Survival Through the End of Study Treatment

| End point title | Percentage of Participants with Fungal-free Survival Through the End of Study Treatment |
|---|---|

End point description:

Fungal-free survival is those participants who survived up to end of study treatment, and had documented microbiological eradication of Candida species (sp.) from follow-up cultures collected after the initiation of study therapy. Microbiological eradication denotes negative follow-up cultures for Candida sp. from the site of infection. If a culture is not obtained on the day of assessment, the last culture after study entry may be used to assist in the assessment of microbiological eradication. If the last culture is negative for Candida sp., then microbiological eradication would be considered achieved. The population analyzed was participants who received at least 1 full dose of study therapy and had a documented (culture-confirmed) diagnosis of invasive candidiasis.

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

End point timeframe:

Up to 90 days

| End point values | Caspofungin | Amphotericin B Deoxycholate | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 31 | 16 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 71.0 (52.0 to 85.8) | 75.0 (47.6 to 92.7) | | |

## Statistical analyses

| Statistical analysis title | Caspofungin minus Amphotericin |
|---|---|

Statistical analysis description:

Miettinen & Nurminen method stratified by stratum (Weight category based on weight at study entry) with Cochran Mantel- Haenszel's weights

| | |
|---|---|
| Comparison groups | Caspofungin v Amphotericin B Deoxycholate |
| Number of subjects included in analysis | 47 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Difference in Percentage |
| Point estimate | -6.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.2 |
| upper limit | 22.6 |

## Secondary: Number of participants with an adverse event (AE)

| | |
|---|---|
| End point title | Number of participants with an adverse event (AE) |

End point description:

An AE is any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR’s product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR’s product, is also an AE. The population analyzed was all participants as treated.

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

End point timeframe:

8 weeks after end of study therapy (up to 146 days)

| End point values | Caspofungin | Amphotericin B Deoxycholate | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 16 | | |
| Units: Participants | 28 | 16 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| 8 weeks after end of study therapy (up to 146 days) | |
| Adverse event reporting additional description: | |
| All participants as treated | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Caspofungin |
| Reporting group description: | |
| Caspofungin 2 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |
| Reporting group title | Amphotericin B deoxycholate |
| Reporting group description: | |
| Amphotericin B deoxycholate 1 mg/kg intravenous once daily for ≥14 days after documented negative culture and improvement of clinical signs and symptoms, for a maximum of 90 days treatment | |

| Serious adverse events | Caspofungin | Amphotericin B deoxycholate | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 33 (21.21%) | 9 / 16 (56.25%) | |
| number of deaths (all causes) | 2 | 3 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Anastomotic complication | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Suture rupture | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Vascular disorders | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising colitis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Infections and infestations | | | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia escherichia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 16 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| **Non-serious adverse events** | Caspofungin | Amphotericin B deoxycholate | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 33 (69.70%) | 15 / 16 (93.75%) | |
| General disorders and administration site conditions | | | |
| Hypothermia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 33 (18.18%) | 3 / 16 (18.75%) | |
| occurrences (all) | 10 | 6 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Apnoea | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 16 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 3 / 16 (18.75%) | |
| occurrences (all) | 0 | 3 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 16 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Blood bilirubin unconjugated increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 3 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Blood potassium increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 16 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 16 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 2 / 16 (12.50%) | |
| occurrences (all) | 0 | 3 | |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 16 (12.50%) | |
| occurrences (all) | 2 | 2 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 16 (6.25%) | |
| occurrences (all) | 5 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 33 (30.30%) | 8 / 16 (50.00%) | |
| occurrences (all) | 16 | 12 | |
| Leukostasis syndrome | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Eye discharge | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 2 / 16 (12.50%) | |
| occurrences (all) | 2 | 2 | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Necrotising enterocolitis neonatal | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 16 (6.25%) | |
| occurrences (all) | 2 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 16 (6.25%) | |
| occurrences (all) | 4 | 2 | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 16 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Glycosuria | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Renal tubular necrosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 5 / 16 (31.25%) | |
| occurrences (all) | 5 | 6 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Metabolism and nutrition disorders | | | |
| Feeding intolerance | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 0 / 16 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypernatraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Hypochloraemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 2 / 16 (12.50%) | |
| occurrences (all) | 3 | 5 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | 1 / 16 (6.25%) | |
| occurrences (all) | 2 | 1 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 3 / 33 (9.09%) | 1 / 16 (6.25%) | |
| occurrences (all) | 3 | 1 | |
| Metabolic alkalosis | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 28 November 2013 | Amendment 1: Revision of pharmacokinetic blood sampling schedule for study participants. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 28 February 2018 | The trial was terminated early due to operational feasibility with low recruitment due to changing epidemiology of disease. | - |

Notes:

### Limitations and caveats

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

| |
|---|
| The trial was terminated early due to operational feasibility with low recruitment due to changing epidemiology of disease. |

Notes: