



## 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
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##### 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
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<b>Arm title</b>	Caspofungin
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Arm description:

Caspofungin 2 mg/kg intravenous once daily for  $\geq 14$  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  $\geq 14$  days

<b>Arm title</b>	Amphotericin B Deoxycholate
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Arm description:

Amphotericin B deoxycholate 1 mg/kg intravenous once daily for  $\geq 14$  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  $\geq 14$  days

<b>Number of subjects in period 1</b>	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 $\geq 14$ 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 $\geq 14$ 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 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 Units: days			
arithmetic mean	31.1	32.8	-
standard deviation	$\pm 20.9$	$\pm 23.3$	
Gender Categorical Units: Subjects			
Female	14	10	24
Male	20	7	27
Race 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 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			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: days			
arithmetic mean			
standard deviation	±	±	
Gender Categorical			
Units: Subjects			
Female			
Male			
Race			
Units: Subjects			
American Indian or Alaska Native			
Black or African American			
White			
More than one race			
Ethnicity			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
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 $\geq 14$ 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 $\geq 14$ 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 $\geq 14$ 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 $\geq 14$ 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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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

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

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End point title	Number of participants with an adverse event (AE)
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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
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End point timeframe:

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

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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

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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### Reporting groups

Reporting group title	Caspofungin
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Reporting group description:

Caspofungin 2 mg/kg intravenous once daily for  $\geq 14$  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
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Reporting group description:

Amphotericin B deoxycholate 1 mg/kg intravenous once daily for  $\geq 14$  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	
<b>Meningitis bacterial</b>			
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	
<b>Pneumonia</b>			
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	
<b>Pneumonia escherichia</b>			
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	
<b>Septic shock</b>			
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 %

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

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



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

subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 16 (6.25%) 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:

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### 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: