



Clinical trial results:

A Multicenter, Double-Blind, Randomized, Comparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Versus (Amphotericin B) Liposome for Injection as Empirical Therapy in Pediatric Patients With Persistent Fever and Neutropenia

Summary

EudraCT number	2014-005021-13
Trial protocol	Outside EU/EEA
Global end of trial date	04 October 2006

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	MK-0991-044
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00082537
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)	Yes
EMA paediatric investigation plan number(s)	EMA-000010-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 October 2006
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2006
Global end of trial reached?	Yes
Global end of trial date	04 October 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate in pediatric patients, aged 2 to 17 years, with persistent fever and neutropenia, the proportion of participants treated with caspofungin reporting one or more clinical and/or laboratory drug-related adverse experience(s) during the study drug therapy period plus 14 days posttherapy.

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.

If drug-related toxicity develops, the dose may be reduced to the standard dose. Any participant who has a body surface area $\geq 1.2 \text{ m}^2$ is not eligible for dose increase for inadequate clinical response because their standard daily dose of caspofungin approaches the maximum dose of 70 mg/day. Therefore, a participant whose dose in the caspofungin arm is $\geq 60 \text{ mg/day}$ (50 mg/m^2 for a 1.2 m^2 participant) and requires dose increase as determined by the investigator, must be discontinued from study therapy.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2004
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	Germany: 18
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Belgium: 14
Worldwide total number of subjects	82
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

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

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	62
Adolescents (12-17 years)	20
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:

A total of 83 participants were screened. One screened participant was randomized but did not receive study therapy.

Period 1

Period 1 title	Treatment and Follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Caspofungin

Arm description:

Participants received 1-hour intravenous infusion of caspofungin 70 mg/m² as a loading dose on Day 1 followed by 50 mg/m² once daily for up to 28 days. On completion of the caspofungin infusion participants received 2-hour intravenous infusion of placebo to liposomal amphotericin B once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Arm type	Experimental
Investigational medicinal product name	Caspofungin
Investigational medicinal product code	
Other name	CANCIDAS™, MK-0991
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 1-hour intravenous infusion of caspofungin acetate 70 mg/m² as a loading dose on Day 1 followed by 50 mg/m² once daily for up to 28 days. Infusion was administered via 1) peripheral line, 2) peripherally inserted central catheter, or 3) other central venous catheter.

Investigational medicinal product name	Placebo to Liposomal Amphotericin B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

On completion of the caspofungin infusion participants received 2-hour intravenous infusion of placebo to liposomal amphotericin B (5% dextrose in water with multivitamin) once daily for up to 28 days. Infusion was administered via 1) peripheral line, 2) peripherally inserted central catheter, or 3) other central venous catheter.

Arm title	Liposomal Amphotericin B
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Arm description:

Participants received 1-hour intravenous infusion of placebo to caspofungin once daily for up to 28 days. On completion of the placebo infusion participants received 2-hour intravenous infusion of liposomal amphotericin B 3.0 mg/kg once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Arm type	Active comparator
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Investigational medicinal product name	Liposomal Amphotericin B
Investigational medicinal product code	
Other name	AmBisome™
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

On completion of the placebo infusion participants received 2-hour intravenous infusion of liposomal amphotericin B 3.0 mg/kg once daily for up to 28 days. Infusion was administered via 1) peripheral line, 2) peripherally inserted central catheter, or 3) other central venous catheter.

Investigational medicinal product name	Placebo to Caspofungin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 1-hour intravenous infusion of placebo to caspofungin (0.9% saline) once daily for up to 28 days. Infusion was administered via 1) peripheral line, 2) peripherally inserted central catheter, or 3) other central venous catheter.

Number of subjects in period 1	Caspofungin	Liposomal Amphotericin B
Started	56	26
Completed study therapy	46 ^[1]	19 ^[2]
Completed	56	25
Not completed	0	1
Adverse event, serious fatal	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants who completed study therapy and continued to follow-up

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants who completed study therapy and continued to follow-up

Baseline characteristics

Reporting groups

Reporting group title	Caspofungin
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Reporting group description:

Participants received 1-hour intravenous infusion of caspofungin 70 mg/m² as a loading dose on Day 1 followed by 50 mg/m² once daily for up to 28 days. On completion of the caspofungin infusion participants received 2-hour intravenous infusion of placebo to liposomal amphotericin B once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Reporting group title	Liposomal Amphotericin B
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Reporting group description:

Participants received 1-hour intravenous infusion of placebo to caspofungin once daily for up to 28 days. On completion of the placebo infusion participants received 2-hour intravenous infusion of liposomal amphotericin B 3.0 mg/kg once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Reporting group values	Caspofungin	Liposomal Amphotericin B	Total
Number of subjects	56	26	82
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	7.4 ± 4.5	7.4 ± 4.9	-
Gender categorical Units: Subjects			
Female	21	6	27
Male	35	20	55

End points

End points reporting groups

Reporting group title	Caspofungin
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Reporting group description:

Participants received 1-hour intravenous infusion of caspofungin 70 mg/m² as a loading dose on Day 1 followed by 50 mg/m² once daily for up to 28 days. On completion of the caspofungin infusion participants received 2-hour intravenous infusion of placebo to liposomal amphotericin B once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Reporting group title	Liposomal Amphotericin B
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Reporting group description:

Participants received 1-hour intravenous infusion of placebo to caspofungin once daily for up to 28 days. On completion of the placebo infusion participants received 2-hour intravenous infusion of liposomal amphotericin B 3.0 mg/kg once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Primary: Percentage of Participants with One or More Drug-related Adverse Experience

End point title	Percentage of Participants with One or More Drug-related Adverse Experience ^[1]
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End point description:

An adverse experience is defined as 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 of a preexisting condition which is temporally associated with the use of the sponsor's product, is also an adverse experience. Drug-related adverse experiences were those determined by the investigator to be possibly, probably, or definitely drug related. The population included all participants who received at least one dose of active study therapy.

End point type	Primary
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End point timeframe:

Up to 14 days after the end of study therapy

Notes:

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

Justification: No between-group statistical analyses were planned for the study.

End point values	Caspofungin	Liposomal Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	26		
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Experiences	48.2	46.2		
Laboratory Adverse Experiences	10.7	19.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with One or More Drug-related Serious

Adverse Experiences

End point title	Percentage of Participants with One or More Drug-related Serious Adverse Experiences
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End point description:

A serious adverse experience is any adverse experience that results in death, is life threatening, results in persistent or significant disability or incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly or birth defect, is a cancer, or is an overdose. Drug-related adverse experiences were those determined by the investigator to be possibly, probably, or definitely drug related. The population included all participants who received at least one dose of active study therapy.

End point type	Secondary
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End point timeframe:

Up to 14 days after the last dose of study therapy

End point values	Caspofungin	Liposomal Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	26		
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Experiences	1.8	11.5		
Laboratory Adverse Experiences	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Discontinued Study Therapy due to a Drug-related Adverse Experience

End point title	Percentage of Participants Who Discontinued Study Therapy due to a Drug-related Adverse Experience
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End point description:

An adverse experience is defined as 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 of a preexisting condition which is temporally associated with the use of the sponsor's product, is also an adverse experience. Drug-related adverse experiences were those determined by the investigator to be possibly, probably, or definitely drug related. The population included all participants who received at least one dose of active study therapy.

End point type	Secondary
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End point timeframe:

Up to the last dose of study therapy

End point values	Caspofungin	Liposomal Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	26		
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Experiences	3.6	11.5		
Laboratory Adverse Experiences	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Favorable Overall Efficacy Outcome

End point title	Percentage of Participants with Favorable Overall Efficacy Outcome
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End point description:

Favorable overall efficacy outcome was defined as meeting each of the following criteria: 1) survival for ≥ 7 days after end of study drug therapy, 2) resolution of fever during the period of neutropenia, 3) for participants with a fungal infection at baseline, successful treatment of the baseline infection, 4) absence of breakthrough fungal infections during administration of study drug or within 7 days after the end of treatment, and 5) absence of premature discontinuation of the study drug because of study-drug-related toxicity or lack of efficacy. The population included participants who received chemotherapy for hematological or solid organ malignancies or hematopoietic stem cell transplant, met the protocol-defined inclusion criteria for fever and neutropenia, and received at least 1 dose of study therapy.

End point type	Secondary
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End point timeframe:

Up to 7 days after the last dose of study therapy

End point values	Caspofungin	Liposomal Amphotericin B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	25		
Units: Percentage of participants				
number (confidence interval 95%)	46.4 (33.4 to 59.5)	32 (13.7 to 50.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 days after the last dose of study drug

Adverse event reporting additional description:

Although a participant may have had two or more clinical adverse events, the participant is counted only once within a category. The same participant may appear in different categories.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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Reporting groups

Reporting group title	Caspofungin
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Reporting group description:

Participants received 1-hour intravenous infusion of caspofungin 70 mg/m² as a loading dose on Day 1 followed by 50 mg/m² once daily for up to 28 days. On completion of the caspofungin infusion participants received 2-hour intravenous infusion of placebo to liposomal amphotericin B once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Reporting group title	Liposomal Amphotericin B
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Reporting group description:

Participants received 1-hour intravenous infusion of placebo to caspofungin once daily for up to 28 days. On completion of the placebo infusion participants received 2-hour intravenous infusion of liposomal amphotericin B 3.0 mg/kg once daily for up to 28 days. Study drug treatment could be for up to 90 days for documented invasive fungal infection.

Serious adverse events	Caspofungin	Liposomal Amphotericin B	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 56 (19.64%)	6 / 26 (23.08%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia recurrent			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 56 (3.57%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngospasm			

subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Caecitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circumoral oedema			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (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 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis adenovirus			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	1 / 56 (1.79%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Caspofungin	Liposomal Amphotericin B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 56 (89.29%)	21 / 26 (80.77%)	
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 56 (7.14%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Hypertension			
subjects affected / exposed	5 / 56 (8.93%)	1 / 26 (3.85%)	
occurrences (all)	5	1	
Hypotension			
subjects affected / exposed	4 / 56 (7.14%)	2 / 26 (7.69%)	
occurrences (all)	4	2	
General disorders and administration site conditions			

Chills			
subjects affected / exposed	7 / 56 (12.50%)	2 / 26 (7.69%)	
occurrences (all)	7	2	
Oedema			
subjects affected / exposed	2 / 56 (3.57%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Pyrexia			
subjects affected / exposed	17 / 56 (30.36%)	6 / 26 (23.08%)	
occurrences (all)	42	14	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	2 / 56 (3.57%)	2 / 26 (7.69%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 56 (8.93%)	2 / 26 (7.69%)	
occurrences (all)	5	2	
Epistaxis			
subjects affected / exposed	3 / 56 (5.36%)	1 / 26 (3.85%)	
occurrences (all)	3	1	
Rhinorrhoea			
subjects affected / exposed	3 / 56 (5.36%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Tachypnoea			
subjects affected / exposed	4 / 56 (7.14%)	1 / 26 (3.85%)	
occurrences (all)	4	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 56 (5.36%)	3 / 26 (11.54%)	
occurrences (all)	5	6	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 56 (1.79%)	3 / 26 (11.54%)	
occurrences (all)	1	6	
Blood potassium decreased			
subjects affected / exposed	5 / 56 (8.93%)	7 / 26 (26.92%)	
occurrences (all)	5	8	

Blood potassium increased subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	2 / 26 (7.69%) 2	
Protein total decreased subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	2 / 26 (7.69%) 5	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 6	4 / 26 (15.38%) 4	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 7	1 / 26 (3.85%) 2	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	2 / 26 (7.69%) 2	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	1 / 26 (3.85%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 2	3 / 26 (11.54%) 3	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	4 / 26 (15.38%) 4	
Nausea subjects affected / exposed occurrences (all)	2 / 56 (3.57%) 3	2 / 26 (7.69%) 11	
Vomiting subjects affected / exposed occurrences (all)	6 / 56 (10.71%) 6	3 / 26 (11.54%) 7	
Skin and subcutaneous tissue disorders Erythema			

subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 5	0 / 26 (0.00%) 0	
Petechiae subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 4	1 / 26 (3.85%) 1	
Pruritus subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 4	2 / 26 (7.69%) 2	
Rash subjects affected / exposed occurrences (all)	13 / 56 (23.21%) 15	2 / 26 (7.69%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	2 / 26 (7.69%) 2	
Infections and infestations Central line infection subjects affected / exposed occurrences (all)	5 / 56 (8.93%) 5	0 / 26 (0.00%) 0	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	1 / 26 (3.85%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported