Clinical trial results:
A Multicenter, Open-Label, Noncomparative Study to Evaluate the Safety, Tolerability, and Efficacy of Caspofungin Acetate in Children with Documented Candida or Aspergillus Infections

Summary

EudraCT number	2014-004911-35
Trial protocol	Outside EU/EEA
Global end of trial date	31 July 2007

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-0991-043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00082524
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)	EMEA-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	31 July 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2007
Global end of trial reached?	Yes
Global end of trial date	31 July 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study are to evaluate the safety, tolerability, and efficacy of caspofungin therapy, administered as 50 mg/m^2 intravenous once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1, in pediatric patients (3 months through 17 years of age) with invasive aspergillosis who are refractory to or intolerant of standard therapy or those with invasive or esophageal Candida infections. The primary objective is to report the proportion of pediatric participants treated with caspofungin with one or more drug-related clinical or laboratory adverse experience(s).

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.

Participants who failed to improve clinically after at least 4 days of caspofungin and in whom the drug had been well-tolerated could receive a dosage increase to 70 mg/m^2 (maximum 70 mg/day) from Day 5 onward. The need to increase the caspofungin dose was at the discretion of the investigator. The higher dose was to be maintained until therapy was discontinued unless toxicity occurred. If drug-related toxicity developed, the dose could be reduced to standard dose (50 mg/m^2).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 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	Israel: 3
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	49
EEA total number of subjects	6

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)	3
Children (2-11 years)	30
Adolescents (12-17 years)	16
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were included based on criteria specific to their fungal infection: invasive Aspergillus infections, invasive Candida infections, or esophageal Candida infections. Other inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

A total of 53 participants were screened and 49 were enrolled in the study.

Period 1

Period 1 title	Treatment and Follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Participants with Invasive Aspergillosis

Arm description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 28 days and for at least 7 days after resolution of symptoms (maximum of 90 days). Follow-up was up to 28 days after the last infusion of study drug.

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:

Caspofungin acetate 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 28 days and for at least 7 days after resolution of symptoms (maximum of 90 days). Follow-up was up to 28 days after the last infusion of study drug. Infusion employed a pediatric syringe or ambulatory pump.

Arm title	Participants with Invasive Candidiasis

Arm description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 14 days after the last positive culture of Candida from the blood or other normally sterile body site, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug.

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:

Caspofungin acetate 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 14 days after the last positive culture of Candida from the blood or other normally sterile body site, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug.

Infusion employed a pediatric syringe or ambulatory pump.

Arm title	Participants with Esophageal Candidiasis

Arm description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 7 days and for at least 72 hours past resolution of symptoms, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug.

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:

Caspofungin acetate 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 7 days and for at least 72 hours past resolution of symptoms, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug. Infusion employed a pediatric syringe or ambulatory pump.

Number of subjects in period 1	Participants with Invasive Aspergillosis	Participants with Invasive Candidiasis	Participants with Esophageal Candidiasis
Started	10	38	1
Completed therapy	5 [1]	23 [2]	1
Completed	6	36	1
Not completed	4	2	0
Adverse event, serious fatal	1	-	-
Participant moved	-	1	-
Adverse event, non-fatal	3	-	-
Unknown	-	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	Participants with Invasive Aspergillosis
Reporting group description:	
Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 28 days and for at least 7 days after resolution of symptoms (maximum of 90 days). Follow-up was up to 28 days after the last infusion of study drug.	
Reporting group title	Participants with Invasive Candidiasis
Reporting group description:	
Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 14 days after the last positive culture of Candida from the blood or other normally sterile body site, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug.	
Reporting group title	Participants with Esophageal Candidiasis
Reporting group description:	
Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 7 days and for at least 72 hours past resolution of symptoms, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug.	

Reporting group values	Participants with Invasive Aspergillosis	Participants with Invasive Candidiasis	Participants with Esophageal Candidiasis
Number of subjects	10	38	1
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	8.3	7.9	17
standard deviation	± 3.9	± 5.4	± 0
Gender categorical			
Units: Subjects			
Female	2	16	0
Male	8	22	1

Reporting group values	Total		
Number of subjects	49		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	18		
Male	31		

End points

End points reporting groups

Reporting group title	Participants with Invasive Aspergillosis

Reporting group description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 28 days and for at least 7 days after resolution of symptoms (maximum of 90 days). Follow-up was up to 28 days after the last infusion of study drug.

Reporting group title	Participants with Invasive Candidiasis

Reporting group description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 14 days after the last positive culture of Candida from the blood or other normally sterile body site, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug.

Reporting group title	Participants with Esophageal Candidiasis

Reporting group description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 7 days and for at least 72 hours past resolution of symptoms, and a maximum of 28 days. Follow-up was up to 28 days after the last infusion of study drug.

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]

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 All Patients as Treated population included all participants who received at least one dose of caspofungin.

End point type	Primary

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	Participants with Invasive Aspergillosis	Participants with Invasive Candidiasis	Participants with Esophageal Candidiasis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	38	1	
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Experiences	40	23.7	0	
Laboratory Adverse Experiences	20	39.5	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

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'd 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 All Patients as Treated population included all participants who received at least one dose of caspofungin.

End point type	Secondary

End point timeframe:

Up to the last dose of study therapy

End point values	Participants with Invasive Aspergillosis	Participants with Invasive Candidiasis	Participants with Esophageal Candidiasis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	38	1	
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Experiences	0	0	0	
Laboratory Adverse Experiences	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with One or More Serious Adverse Experiences

End point title	Percentage of Participants with One or More Serious Adverse Experiences

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. The All Patients as Treated population included all participants who received at least one dose of caspofungin.

End point type	Secondary

End point timeframe:

Up to 14 days after the end of study therapy.

End point values	Participants with Invasive Aspergillosis	Participants with Invasive Candidiasis	Participants with Esophageal Candidiasis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	38	1	
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Experiences	50	7.9	0	
Laboratory Adverse Experiences	0	0	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Invasive Aspergillosis Participants with a Favorable Clinical Response

End point title	Percentage of Invasive Aspergillosis Participants with a Favorable Clinical Response[2]

End point description:

Favorable clinical response was defined as clinically significant improvement or resolution of symptoms and radiographic and other relevant investigative (eg, bronchoscopy) abnormalities attributable to Aspergillus infection. The Modified Intent-to-Treat population included participants who received at least 1 full dose of caspofungin therapy and had documented diagnosis of invasive aspergillosis.

End point type	Secondary

End point timeframe:

Last day of study therapy (at least 7 days after resolution of symptoms)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint analyzes only participants with invasive aspergillosis.

End point values	Participants with Invasive Aspergillosis			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of participants				
number (confidence interval 95%)	50 (18.7 to 81.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Invasive Candidiasis Participants with a Favorable Overall Response

End point title	Percentage of Invasive Candidiasis Participants with a Favorable Overall Response[3]

End point description:

Favorable overall response was defined as 1) resolution or improvement of most signs and symptoms of the invasive Candida infection and resolution or improvement of all relevant radiographic findings (if previously present), and 2) follow-up cultures from site of infection are negative for Candida or, for infections which would require an invasive procedure for documentation of a follow-up negative culture, no apparent evidence of residual infection from symptoms, physical examination, and appropriate non-invasive studies (laboratory test, imaging, etc). The Modified Intent-to-Treat population included participants who received at least 1 full dose of caspofungin therapy and had documented diagnosis of invasive candidiasis.

End point type	Secondary

End point timeframe:

Last day of study therapy (up to 28 days)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint analyzes only participants with invasive candidiasis.

End point values	Participants with Invasive Candidiasis			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percentage of participants				
number (confidence interval 95%)	81.1 (64.8 to 92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Esophageal Candidiasis Participants with Favorable Clinical Response

End point title	Percentage of Esophageal Candidiasis Participants with Favorable Clinical Response[4]

End point description:

Favorable clinical response was defined as 1) resolution, or reduction of endoscopic lesions by at least one stepwise grade (or no endoscopy performed), and 2) resolution or improvement of esophageal signs / symptoms from the baseline findings. The Modified Intent-to-Treat population included participants who received at least 1 full dose of caspofungin therapy and had documented diagnosis of esophageal candidiasis.

End point type	Secondary

End point timeframe:

Last day of study therapy (up to 28 days)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint analyzes only participants with esophageal candidiasis.

End point values	Participants with Esophageal Candidiasis			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of participants				
number (not applicable)	100			

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 end of study therapy

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Participants with Invasive Aspergillosis

Reporting group description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 28 days and for at least 7 days after resolution of symptoms. Follow-up was for 28 days after the last infusion of study drug.

Reporting group title	Participants with Invasive Candidiasis

Reporting group description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 14 days after the last positive culture of Candida from the blood or other normally sterile body site, and a maximum of 28 days. Follow-up was for 28 days after the last infusion of study drug.

Reporting group title	Participants with Esophageal Candidiasis

Reporting group description:

Participants received caspofungin 50 mg/m^2 in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m^2 (maximum 70 mg/day) on Day 1. Duration of therapy was for a minimum of 14 days and for at least 72 hours past resolution of symptoms, and a maximum of 28 days. Follow-up was for 28 days after the last infusion of study drug.

Serious adverse events	Participants with Invasive Aspergillosis	Participants with Invasive Candidiasis	Participants with Esophageal Candidiasis
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	3 / 38 (7.89%)	1 / 1 (100.00%)
number of deaths (all causes)	5	0	0
number of deaths resulting from adverse events			
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 38 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Acute lymphocytic leukaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myeloid leukaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			

subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 10 (0.00%)	1 / 38 (2.63%)	0 / 1 (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
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fungal sepsis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic embolus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Zygomycosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 38 (2.63%)	0 / 1 (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: 5 %

Non-serious adverse events	Participants with Invasive Aspergillosis	Participants with Invasive Candidiasis	Participants with Esophageal Candidiasis
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	33 / 38 (86.84%)	0 / 1 (0.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	5 / 38 (13.16%)	0 / 1 (0.00%)
occurrences (all)	0	5	0
Hypotension			
subjects affected / exposed	2 / 10 (20.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	3	3	0
Phlebitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Crepitations			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Oedema			

subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	5 / 38 (13.16%)	0 / 1 (0.00%)
occurrences (all)	3	7	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Hypoxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Pleurisy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Pulmonary hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Rales			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Respiratory distress			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Respiratory failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Tachypnoea			

subjects affected / exposed	1 / 10 (10.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	6 / 38 (15.79%)	0 / 1 (0.00%)
occurrences (all)	17	7	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	9 / 38 (23.68%)	0 / 1 (0.00%)
occurrences (all)	17	9	0
Bacteria urine identified			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Band neutrophil count increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
Bilirubin conjugated increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	4	3	0
Blood bicarbonate increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	8	0	0
Blood bilirubin increased			
subjects affected / exposed	4 / 10 (40.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	7	1	0
Blood calcium decreased			

subjects affected / exposed	2 / 10 (20.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Blood chloride increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	3	1	0
Blood glucose increased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 38 (7.89%)	0 / 1 (0.00%)
occurrences (all)	0	3	0
Blood magnesium decreased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 38 (7.89%)	0 / 1 (0.00%)
occurrences (all)	0	3	0
Blood phosphorus decreased			
subjects affected / exposed	2 / 10 (20.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	4	2	0
Blood phosphorus increased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 38 (7.89%)	0 / 1 (0.00%)
occurrences (all)	0	3	0
Blood potassium decreased			
subjects affected / exposed	4 / 10 (40.00%)	8 / 38 (21.05%)	0 / 1 (0.00%)
occurrences (all)	8	10	0
Blood potassium increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Blood sodium increased			
subjects affected / exposed	2 / 10 (20.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	4	2	0
Blood urea increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
Blood uric acid decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Breath sounds abnormal			

subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Eosinophil count increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	5	7	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	4 / 38 (10.53%)	0 / 1 (0.00%)
occurrences (all)	0	4	0
Haematocrit decreased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Haemoglobin decreased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 38 (7.89%)	0 / 1 (0.00%)
occurrences (all)	0	4	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Oxygen saturation decreased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Platelet count decreased			
subjects affected / exposed	1 / 10 (10.00%)	3 / 38 (7.89%)	0 / 1 (0.00%)
occurrences (all)	1	6	0
Platelet count increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	4	0
Prothrombin time prolonged			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
White blood cell count increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			

Feeding tube complication			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Cardiac failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 38 (7.89%)	0 / 1 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Hypotonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Lymphadenopathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	2	1	0

Constipation			
subjects affected / exposed	1 / 10 (10.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	3 / 10 (30.00%)	3 / 38 (7.89%)	0 / 1 (0.00%)
occurrences (all)	3	3	0
Lip dry			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	2 / 10 (20.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	3	2	0
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	2 / 10 (20.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	2	2	0
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Rash			

subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Rash papular			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
Skin nodule			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 38 (2.63%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus infection			
subjects affected / exposed	2 / 10 (20.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Fungal sepsis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			

subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 38 (5.26%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Anorexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Diabetes mellitus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Fluid retention			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Magnesium deficiency			
subjects affected / exposed	1 / 10 (10.00%)	0 / 38 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2006	Protocol Amendment MK-0991-043-01 included the following changes: 1) personnel contact information was updated to reflect current telephone numbers, fax numbers, email addresses, and mailing addresses, 2) the Background section was shortened to provide only new and the most relevant information. The reader is referred to the Product Package Insert and the Confidential Investigator's Brochure (CIB) for detailed background information, 3) the included age range was expanded from patients aged 2 to 17 years to patients aged 3 months to 17 years and a rationale for this change was added, 4) instructions for collection of blood samples for pharmacokinetic (PK) analysis were modified. Five-point PK sampling on Day 4 is required for all patients aged 3 months to <24 months while for patients aged 24 months to 17 years only a subset of sites will perform 5-point sampling on Day 4., 5) the wording under Section I. E. 2. 3 Infusion of Caspofungin has been updated, 6) the estimated overall duration of the study was increased to 36 months and an interim report is now planned, 7) the List of References was updated, 8) several appendices were restructured to clarify the procedures for processing and shipping of fungal isolates and PK samples. "Recommended Volume" has been replaced with "Maximum Volume" in APPENDIX 7, 9) minor typographical errors were corrected. Additional wording changes were made for clarity but these did not alter the intent of the content of the original protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported