



## Clinical trial results:

### **A Multicenter, Open, Sequential Dose-Escalation Study to Investigate the Safety, Tolerability, and Pharmacokinetics of 2 Separate Doses of Caspofungin Acetate in Children Between the Ages of 3 to 24 Months With New Onset Fever and Neutropenia**

#### **Summary**

EudraCT number	2014-005030-54
Trial protocol	Outside EU/EEA
Global end of trial date	31 July 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-0991-042
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00292071
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?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	31 July 2006
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2006
Global end of trial reached?	Yes
Global end of trial date	31 July 2006
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

This study was an open-label, multicenter study to evaluate the safety, tolerability, and pharmacokinetics of caspofungin in clinically stable children with fever and neutropenia between the ages of 3 to 24 months.

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.

Caspofungin was to be administered daily until the participant recovered from the neutropenic episode. However, if the participant remained febrile and neutropenic after 4 days of therapy, caspofungin was to be discontinued and the participant was to be started thereafter on a standard empirical antifungal regimen with intravenous amphotericin B (either conventional deoxycholate or a lipid formulation). Similarly, if the participant developed a proven or probable breakthrough invasive fungal infection, caspofungin was to be discontinued and an intravenous (IV) formulation of amphotericin B was to be administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	9

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:

The study enrolled clinically stable, immunocompromised children between the ages of 3 and 24 months with a history of underlying hematological or solid organ malignancies, hematopoietic stem cell transplantation (including bone marrow or peripheral stem cell transplantation), or aplastic anemia, and new onset fever and neutropenia.

### Pre-assignment

Screening details:

Nine participants were screened and 9 were enrolled in the study. Only the caspofungin 50 mg/m<sup>2</sup>/day regimen was enrolled. Due to enrollment difficulties the study was halted prior to enrollment of any participants in the caspofungin 70 mg/m<sup>2</sup>/day regimen.

### Period 1

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

### Arms

<b>Arm title</b>	Caspofungin 50 mg/m <sup>2</sup> /day
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Arm description:

Participants received caspofungin 50 mg/m<sup>2</sup>/day in a 1-hour intravenous infusion for a minimum of 4 days and a maximum of 28 days.

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<sup>2</sup>/day in a 1-hour intravenous infusion for a minimum of 4 days and a maximum of 28 days. Infusion employed a pediatric syringe or ambulatory pump.

<b>Number of subjects in period 1</b>	Caspofungin 50 mg/m <sup>2</sup> /day
Started	9
Completed	8
Not completed	1
Adverse event, serious fatal	1

## Baseline characteristics

### Reporting groups

Reporting group title	Caspofungin 50 mg/m <sup>2</sup> /day
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Reporting group description:

Participants received caspofungin 50 mg/m<sup>2</sup>/day in a 1-hour intravenous infusion for a minimum of 4 days and a maximum of 28 days.

Reporting group values	Caspofungin 50 mg/m <sup>2</sup> /day	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
7 to 12 months	4	4	
13 to 18 months	3	3	
19 to 24 months	2	2	
Age continuous Units: months			
arithmetic mean	15		
standard deviation	± 4.2	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	6	6	

## End points

### End points reporting groups

Reporting group title	Caspofungin 50 mg/m <sup>2</sup> /day
Reporting group description: Participants received caspofungin 50 mg/m <sup>2</sup> /day in a 1-hour intravenous infusion for a minimum of 4 days and a maximum of 28 days.	

### Primary: Area Under the Plasma Concentration Curve of Caspofungin up to 24 Hours (AUC0-24) on Day 1

End point title	Area Under the Plasma Concentration Curve of Caspofungin up to 24 Hours (AUC0-24) on Day 1 <sup>[1]</sup>
End point description: Plasma caspofungin concentrations were measured with a high-performance liquid chromatography method.	
End point type	Primary
End point timeframe: Plasma samples for measurement of caspofungin concentrations were collected on Day 1 before dosing and at 1, 2, 4, 8, 12, and 24 hours after initiation of the 1-hour infusion.	

#### 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: This was a single-arm study; therefore, no statistical analysis was performed for this endpoint.

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	7 <sup>[2]</sup>			
Units: µg*hr/mL				
least squares mean (confidence interval 95%)	120.2 (100.93 to 143.15)			

#### Notes:

[2] - Participants who received the Day 1 infusion and had sufficient plasma concentration data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Caspofungin at One Hour (C1hr) on Day 1

End point title	Plasma Concentration of Caspofungin at One Hour (C1hr) on Day 1
End point description: Plasma caspofungin concentrations were measured with a high-performance liquid chromatography method.	
End point type	Secondary
End point timeframe: Plasma samples for measurement of caspofungin concentrations were collected on Day 1 before dosing and at 1, 2, 4, 8, 12, and 24 hours after initiation of the 1-hour infusion.	

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	9 <sup>[3]</sup>			
Units: µg/mL				
least squares mean (confidence interval 95%)	17.46 (14.75 to 20.68)			

Notes:

[3] - Participants who received the Day 1 infusion and had sufficient plasma concentration data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Caspofungin at 24 Hours (C24hr) on Day 1

End point title	Plasma Concentration of Caspofungin at 24 Hours (C24hr) on Day 1
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End point description:

Plasma caspofungin concentrations were measured with a high-performance liquid chromatography method.

End point type	Secondary
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End point timeframe:

Plasma samples for measurement of caspofungin concentrations were collected on Day 1 before dosing and at 1, 2, 4, 8, 12, and 24 hours after initiation of the 1-hour infusion.

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	7 <sup>[4]</sup>			
Units: µg/mL				
least squares mean (confidence interval 95%)	1.34 (1.03 to 1.76)			

Notes:

[4] - Participants who received the Day 1 infusion and had sufficient plasma concentration data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration Curve of Caspofungin up to 24 Hours (AUC0-24) on Day 3 to 14

End point title	Area Under the Plasma Concentration Curve of Caspofungin up to 24 Hours (AUC0-24) on Day 3 to 14
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End point description:

Plasma caspofungin concentrations were measured with a high-performance liquid chromatography method. Values reported are for Day 4 or time-average geometric mean of all values obtained between Day 3 and 14.

End point type	Secondary
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End point timeframe:

Plasma samples for measurement of caspofungin concentrations were collected on Day 3 through 14 before dosing and at 1, 2, 4, 8, 12, and 24 hours after initiation of the daily 1-hour infusion.

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	8 <sup>[5]</sup>			
Units: µg*hr/mL				
least squares mean (confidence interval 95%)	130.29 (107.46 to 157.96)			

Notes:

[5] - Participants who received ≥1 infusion on Days 3 - 14 and had sufficient plasma concentration data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Caspofungin at One Hour (C1hr) on Day 3 to 14

End point title	Plasma Concentration of Caspofungin at One Hour (C1hr) on Day 3 to 14
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End point description:

Plasma caspofungin concentrations were measured with a high-performance liquid chromatography method. Values reported are for Day 4 or time-average geometric mean of all values obtained between Day 3 and 14.

End point type	Secondary
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End point timeframe:

Plasma samples for measurement of caspofungin concentrations were collected on Day 3 through 14 before dosing and at 1, 2, 4, 8, 12, and 24 hours after initiation of the daily 1-hour infusion.

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	8 <sup>[6]</sup>			
Units: µg/mL				
least squares mean (confidence interval 95%)	17.21 (14.56 to 20.36)			

Notes:

[6] - Participants who received ≥1 infusion on Days 3 - 14 and had sufficient plasma concentration data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Caspofungin at 24 Hours (C24hr) on Day 3 to 14

End point title	Plasma Concentration of Caspofungin at 24 Hours (C24hr) on Day 3 to 14
End point description:	Plasma caspofungin concentrations were measured with a high-performance liquid chromatography method. Values reported are for Day 4 or time-average geometric mean of all values obtained between Day 3 and 14.
End point type	Secondary
End point timeframe:	Plasma samples for measurement of caspofungin concentrations were collected on Day 3 through 14 before dosing and at 1, 2, 4, 8, 12, and 24 hours after initiation of the daily 1-hour infusion.

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	8 <sup>[7]</sup>			
Units: µg/mL				
least squares mean (confidence interval 95%)	1.64 (1.24 to 2.16)			

Notes:

[7] - Participants who received ≥1 infusion on Days 3 - 14 and had sufficient plasma concentration data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with One or More Adverse Events

End point title	Percentage of Participants with One or More Adverse Events
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 study drug, 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 product, is also an adverse experience.
End point type	Secondary
End point timeframe:	Up to 14 days after the last dose of study drug

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Events	77.8			
Laboratory Adverse Events	55.6			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Discontinued Due to an Adverse Event

End point title	Percentage of Participants Discontinued Due to an Adverse Event
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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 study drug, 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 product, is also an adverse experience.

End point type	Secondary
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End point timeframe:

Up to 14 days after the last dose of study drug

<b>End point values</b>	Caspofungin 50 mg/m <sup>2</sup> /day			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of participants				
number (not applicable)				
Clinical Adverse Event	0			
Laboratory Adverse Event	0			

## 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

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	Caspofungin 50 mg/m <sup>2</sup> /day
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Reporting group description:

Participants received caspofungin 50 mg/m<sup>2</sup>/day in a 1-hour intravenous infusion for a minimum of 4 days and a maximum of 28 days.

<b>Serious adverse events</b>	Caspofungin 50 mg/m <sup>2</sup> /day		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Drug prescribing error			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia cytomegaloviral			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

<b>Non-serious adverse events</b>	Caspofungin 50 mg/m <sup>2</sup> /day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Immune system disorders			
Acute graft versus host disease in skin			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Aspartate aminotransferase			

increased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Blood albumin decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Blood calcium decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood glucose increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Blood magnesium decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood phosphorus decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood sodium increased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Blood uric acid decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Haemoglobin decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Prothrombin time prolonged			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		

White blood cell count increased subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 6		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Nervous system disorders Hydrocephalus subjects affected / exposed occurrences (all)  Intracranial pressure increased subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1  1 / 9 (11.11%) 1		
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Gastrointestinal haemorrhage subjects affected / exposed occurrences (all)  Lip blister subjects affected / exposed occurrences (all)  Mouth haemorrhage subjects affected / exposed occurrences (all)  Mouth plaque subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1  2 / 9 (22.22%) 2  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1		

Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Hepatobiliary disorders Hepatosplenomegaly subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all)  Pruritus subjects affected / exposed occurrences (all)  Rash maculo-papular subjects affected / exposed occurrences (all)  Rash papular subjects affected / exposed occurrences (all)  Skin disorder subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1		
Renal and urinary disorders Acute prerenal failure subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Infections and infestations Candida nappy rash subjects affected / exposed occurrences (all)  Central line infection subjects affected / exposed occurrences (all)  Fungal infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1  1 / 9 (11.11%) 1  1 / 9 (11.11%) 1		

Metabolism and nutrition disorders Metabolic acidosis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
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## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported