



## Clinical trial results:

### A Multicenter, Noncomparative, Open-label Study to Estimate the Safety, Efficacy, and Pharmacokinetics of MK-0991 (Caspofungin) in Japanese Children and Adolescents with Documented Candida or Aspergillus Infections

#### Summary

EudraCT number	2014-004910-27
Trial protocol	Outside EU/EEA
Global end of trial date	17 September 2013

#### Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	09 July 2015

#### Trial information

##### Trial identification

Sponsor protocol code	0991-074
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01165320
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	17 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2013
Global end of trial reached?	Yes
Global end of trial date	17 September 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The study estimates the safety, efficacy, and pharmacokinetics of caspofungin (MK-0991) in Japanese children and adolescents with documented Candida or Aspergillus infections.

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	06 July 2010
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	Japan: 20
Worldwide total number of subjects	20
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)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	11
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants with documented esophageal candidiasis, invasive candidiasis, or aspergillosis and who met all of the additional inclusion and exclusion criteria were to be enrolled in the study.

### Pre-assignment

Screening details:

Three participants were initially enrolled but were withdrawn when their suspected fungal infections were not confirmed. These 3 participants did not receive study drug. No participants with esophageal candidiasis were identified for inclusion in the study.

### Period 1

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

Blinding implementation details:

This was an open-label study.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Participants with Invasive Candidiasis

Arm description:

Caspofungin therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 56 days, respectively.

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 therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily).

<b>Arm title</b>	Participants with Aspergillosis
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Arm description:

Caspofungin therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 84 days, respectively.

Arm type	Experimental
Investigational medicinal product name	Caspofungin
Investigational medicinal product code	
Other name	CANCIDAS®, MK-0991
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Routes of administration	Intravenous use

Dosage and administration details:

Caspofungin therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily).

<b>Number of subjects in period 1</b>	Participants with Invasive Candidiasis	Participants with Aspergillosis
Started	12	8
Completed	9	4
Not completed	3	4
Clinical adverse experience	2	1
Reason unknown	-	1
Laboratory adverse experience	1	-
Lack of efficacy	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Participants with Invasive Candidiasis
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Reporting group description:

Caspofungin therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 56 days, respectively.

Reporting group title	Participants with Aspergillosis
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Reporting group description:

Caspofungin therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 84 days, respectively.

Reporting group values	Participants with Invasive Candidiasis	Participants with Aspergillosis	Total
Number of subjects	12	8	20
Age, Customized Units: Participants			
>=3 months and <2 years	0	1	1
>=2 years and <12 years	8	3	11
>=12 years and <18 years	4	4	8
Age Continuous Units: Years			
arithmetic mean	9.8	9.8	
standard deviation	± 5.2	± 5.2	-
Gender, Male/Female Units: Participants			
Female	9	6	15
Male	3	2	5

## End points

### End points reporting groups

Reporting group title	Participants with Invasive Candidiasis
Reporting group description: Caspofungin therapy as a single loading dose of 70 mg/m <sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m <sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 56 days, respectively.	
Reporting group title	Participants with Aspergillosis
Reporting group description: Caspofungin therapy as a single loading dose of 70 mg/m <sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m <sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 84 days, respectively.	

### Primary: Percentage of Participants with an Overall Favorable Response to Therapy

End point title	Percentage of Participants with an Overall Favorable Response to Therapy <sup>[1]</sup>
End point description: Invasive candidiasis: favorable overall response required resolved clinical findings and negative culture test for Candida species on follow-up. If Candida species were not observed in the baseline blood culture, favorable overall response required resolved clinical findings and resolved or improved radiographic findings. Aspergillosis: favorable overall response required resolved, improved, or unchanged clinical findings and resolved or improved radiographic findings, or resolved or improved clinical findings and resolved, improved, or stable radiographic findings.	
End point type	Primary
End point timeframe: Invasive candidiasis: up to 56 days; aspergillosis: up to 84 days	
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: Per protocol, only descriptive statistics were presented.	

End point values	Participants with Invasive Candidiasis	Participants with Aspergillosis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: Percentage of Participants				
number (not applicable)	66.7	62.5		

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants with One or More Drug-Related Adverse Experiences

End point title	Percentage of Participants with One or More Drug-Related Adverse Experiences <sup>[2]</sup>
End point description: An adverse experience (AE) is defined as any unfavorable or unintended change in the structure,	

function, or chemistry of the body temporally associated with the use of the study drug. Any worsening of a preexisting condition which is temporally associated with the use of the study drug is also an AE. A drug-related AE is one judged to be definitely, probably, or possibly related to the study drug.

End point type	Primary
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End point timeframe:

Invasive candidiasis: up to 70 days; aspergillosis: up to 98 days

Notes:

[2] - 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: Per protocol, only descriptive statistics were presented.

End point values	Participants with Invasive Candidiasis	Participants with Aspergillosis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: Percentage of Participants				
number (not applicable)	58.3	37.5		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 56 days for invasive candidiasis; up to 84 days for aspergillosis

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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### Reporting groups

Reporting group title	Aspergillosis
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Reporting group description:

Caspofungin therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 84 days, respectively.

Reporting group title	Invasive candidiasis
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Reporting group description:

Caspofungin therapy as a single loading dose of 70 mg/m<sup>2</sup> intravenously on Day 1 (maximum not to exceed 70 mg), followed by 50 mg/m<sup>2</sup> as a single once-daily dose on all subsequent days (maximum of 70 mg daily). The minimum and maximum treatment duration was 14 and 56 days, respectively.

Serious adverse events	Aspergillosis	Invasive candidiasis	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	1 / 12 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (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	1 / 8 (12.50%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Aspergillosis	Invasive candidiasis	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	10 / 12 (83.33%)	
Vascular disorders			
Angiopathy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Venoocclusive Disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Puncture Site Pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	4	
Vessel Puncture Site Inflammation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Pulmonary Oedema subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Upper Respiratory Tract Inflammation subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 12 (0.00%) 0	
Investigations			
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	4 / 12 (33.33%) 5	
Aspartate Aminotransferase Increased subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	3 / 12 (25.00%) 4	
Blood Lactate Dehydrogenase Increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 12 (16.67%) 2	
Blood Bilirubin Increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Blood Urine Present subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
C-Reactive Protein Increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Gamma-Glutamyltransferase Increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	3 / 12 (25.00%) 3	
Heart Rate Increased subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 12 (0.00%) 0	
Platelet Count Increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	

White Blood Cell Count Increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Excoriation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 12 (16.67%) 3	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Bone Marrow Failure subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Febrile Neutropenia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Eye disorders Ocular Icterus subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Abdominal Pain			

subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Hypoaesthesia Oral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	3 / 12 (25.00%)	
occurrences (all)	0	4	
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	1 / 8 (12.50%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 8 (12.50%)	4 / 12 (33.33%)	
occurrences (all)	1	7	
Renal and urinary disorders			
Renal Impairment			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

Myalgia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	
Infections and infestations			
Bacterial Infection subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 12 (0.00%) 0	
Pseudomembranous Colitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 12 (0.00%) 0	
Metabolism and nutrition disorders			
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 12 (0.00%) 0	
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 12 (8.33%) 1	

## **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