



## 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.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>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                       | 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<sup>2</sup> intravenous once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<sup>2</sup> (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<sup>2</sup>).

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:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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                                      |
| <b>Arm title</b>             | Participants with Invasive Aspergillosis |

Arm description:

Participants received caspofungin 50 mg/m<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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.

|                  |                                        |
|------------------|----------------------------------------|
| <b>Arm title</b> | Participants with Invasive Candidiasis |
|------------------|----------------------------------------|

Arm description:

Participants received caspofungin 50 mg/m<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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.

|                                                                                                                                                                                                                                                                                                                                                                                                                               |                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| <b>Arm title</b>                                                                                                                                                                                                                                                                                                                                                                                                              | Participants with Esophageal Candidiasis |
| Arm description:<br>Participants received caspofungin 50 mg/m <sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m <sup>2</sup> (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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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 <sup>[1]</sup>                         | 23 <sup>[2]</sup>                      | 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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<br>Units: Subjects |                                          |                                        |                                          |

|                                                                         |              |              |           |
|-------------------------------------------------------------------------|--------------|--------------|-----------|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 8.3<br>± 3.9 | 7.9<br>± 5.4 | 17<br>± 0 |
| Gender categorical<br>Units: Subjects                                   |              |              |           |
| Female                                                                  | 2            | 16           | 0         |
| Male                                                                    | 8            | 22           | 1         |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 49    |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|                                                                         |    |  |  |
|-------------------------------------------------------------------------|----|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -  |  |  |
| Gender categorical<br>Units: Subjects                                   |    |  |  |
| Female                                                                  | 18 |  |  |
| Male                                                                    | 31 |  |  |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Participants with Invasive Aspergillosis |
| Reporting group description:<br>Participants received caspofungin 50 mg/m <sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m <sup>2</sup> (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:<br>Participants received caspofungin 50 mg/m <sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m <sup>2</sup> (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:<br>Participants received caspofungin 50 mg/m <sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m <sup>2</sup> (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 <sup>[1]</sup> |
| End point description:<br>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:<br>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'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 | 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 <sup>[2]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------|

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 <sup>[3]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------|

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.

|                                   |                                        |  |  |  |
|-----------------------------------|----------------------------------------|--|--|--|
| <b>End point values</b>           | 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 <sup>[4]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------|

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.

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

### Statistical analyses

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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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<sup>2</sup> in a 1-hour intravenous infusion once daily (maximum 70 mg/day) following a loading dose of 70 mg/m<sup>2</sup> (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<br>subjects affected / exposed | 1 / 10 (10.00%) | 0 / 38 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all              | 0 / 1           | 0 / 0          | 0 / 0         |
| Acute lymphocytic leukaemia<br>recurrent                   |                 |                |               |
| subjects affected / exposed                                | 1 / 10 (10.00%) | 0 / 38 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to<br>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<br>treatment / all         | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all              | 0 / 1           | 0 / 0          | 0 / 0         |
| Injury, poisoning and procedural<br>complications          |                 |                |               |
| Spinal compression fracture                                |                 |                |               |
| subjects affected / exposed                                | 1 / 10 (10.00%) | 0 / 38 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to<br>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<br>treatment / all         | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0          | 0 / 0         |
| General disorders and administration<br>site conditions    |                 |                |               |
| Multi-organ failure                                        |                 |                |               |
| subjects affected / exposed                                | 1 / 10 (10.00%) | 0 / 38 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to<br>treatment / all              | 0 / 1           | 0 / 0          | 0 / 0         |
| Respiratory, thoracic and mediastinal<br>disorders         |                 |                |               |
| Pneumothorax                                               |                 |                |               |
| subjects affected / exposed                                | 1 / 10 (10.00%) | 0 / 38 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 0          | 0 / 0         |
| deaths causally related to<br>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 %

| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all)                                                                      | 1 / 10 (10.00%)<br>1  | 2 / 38 (5.26%)<br>2  | 0 / 1 (0.00%)<br>0 |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 10 (0.00%)<br>0   | 2 / 38 (5.26%)<br>2  | 0 / 1 (0.00%)<br>0 |
| Investigations<br>Activated partial thromboplastin time prolonged<br>subjects affected / exposed<br>occurrences (all) | 1 / 10 (10.00%)<br>1  | 0 / 38 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 10 (20.00%)<br>17 | 6 / 38 (15.79%)<br>7 | 0 / 1 (0.00%)<br>0 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                              | 2 / 10 (20.00%)<br>17 | 9 / 38 (23.68%)<br>9 | 0 / 1 (0.00%)<br>0 |
| Bacteria urine identified<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 10 (0.00%)<br>0   | 2 / 38 (5.26%)<br>2  | 0 / 1 (0.00%)<br>0 |
| Band neutrophil count increased<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 10 (10.00%)<br>1  | 2 / 38 (5.26%)<br>2  | 0 / 1 (0.00%)<br>0 |
| Bilirubin conjugated increased<br>subjects affected / exposed<br>occurrences (all)                                    | 2 / 10 (20.00%)<br>4  | 0 / 38 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 10 (10.00%)<br>4  | 1 / 38 (2.63%)<br>3  | 0 / 1 (0.00%)<br>0 |
| Blood bicarbonate increased<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 10 (20.00%)<br>8  | 0 / 38 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)                                         | 4 / 10 (40.00%)<br>7  | 1 / 38 (2.63%)<br>1  | 0 / 1 (0.00%)<br>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<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 2 / 38 (5.26%)<br>2 | 0 / 1 (0.00%)<br>0 |
| Cardiac disorders                                                             |                      |                     |                    |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 10 (0.00%)<br>0  | 2 / 38 (5.26%)<br>2 | 0 / 1 (0.00%)<br>0 |
| Cardiac failure<br>subjects affected / exposed<br>occurrences (all)           | 1 / 10 (10.00%)<br>1 | 0 / 38 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Sinus tachycardia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 10 (10.00%)<br>1 | 1 / 38 (2.63%)<br>1 | 0 / 1 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 10 (0.00%)<br>0  | 3 / 38 (7.89%)<br>3 | 0 / 1 (0.00%)<br>0 |
| Nervous system disorders                                                      |                      |                     |                    |
| Convulsion<br>subjects affected / exposed<br>occurrences (all)                | 1 / 10 (10.00%)<br>1 | 0 / 38 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 10 (20.00%)<br>2 | 0 / 38 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Hypotonia<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 10 (10.00%)<br>1 | 0 / 38 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Blood and lymphatic system disorders                                          |                      |                     |                    |
| Coagulopathy<br>subjects affected / exposed<br>occurrences (all)              | 1 / 10 (10.00%)<br>1 | 1 / 38 (2.63%)<br>1 | 0 / 1 (0.00%)<br>0 |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)           | 1 / 10 (10.00%)<br>1 | 0 / 38 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 |
| Gastrointestinal disorders                                                    |                      |                     |                    |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)            | 2 / 10 (20.00%)<br>2 | 1 / 38 (2.63%)<br>1 | 0 / 1 (0.00%)<br>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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported