



## Clinical trial results:

### Determination of Plasmatic and CSF Levels of High Doses of Micafungin in Neonates Suffering from Systemic Candidiasis and/or Candida Meningitis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-003087-20 |
| Trial protocol           | IT             |
| Global end of trial date | 10 April 2018  |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 11 December 2020 |
| First version publication date | 18 October 2018  |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 9463-CL-6001 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03421002 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Astellas Pharma Global Development, Inc. (APGD)  |
| Sponsor organisation address | 1 Astellas Way, Northbrook, United States, 60062   |
| Public contact               | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), <a href="mailto:astellas.resultsdisclosure@astellas.com">astellas.resultsdisclosure@astellas.com</a> |
| Scientific contact           | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), <a href="mailto:astellas.resultsdisclosure@astellas.com">astellas.resultsdisclosure@astellas.com</a> |

Notes:

#### Paediatric regulatory details

|  |     |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No  |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 24 January 2018 |
| Is this the analysis of the primary completion data? | No              |

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|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 10 April 2018 |
| Was the trial ended prematurely? | No            |

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of this study was to study pharmacokinetic (PK) profile of micafungin administered at a dose of 8 mg/kg per day to infants suffering from systemic candidiasis.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 30 May 2015 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 35 |
| Worldwide total number of subjects   | 35        |
| EEA total number of subjects         | 35        |

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Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 8  |
| Infants and toddlers (28 days-23 months)  | 27 |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |

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|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Infant participants with Systemic Candidiasis and/or Candida Meningitis were enrolled in this study.

### Pre-assignment

Screening details:

Eligible participants who met inclusion criteria and none of the exclusion criteria were enrolled. A total of 35 participants were enrolled in this study.

### Period 1

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

### Arms

|           |            |
|-----------|------------|
| Arm title | Micafungin |
|-----------|------------|

Arm description:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour. Micafungin was administered for a minimum of 14 days until 1 of the following conditions applied:

- Negative results (absence of Candida growth) from at least 2 consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level (< 125 pg/mL) were obtained.
- In case of meningitis, hydrocephalus and external ventricular derivation, negative results (absence of Candida growth) from at least 2 consecutive cerebral spinal fluid (CSF) cultures associated with resolution of clinical and laboratory symptoms.
- Interruption (including addition or switch to another antifungal agent or dosage change of micafungin) due to demonstration of therapy failure.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Micafungin            |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour.

| Number of subjects in period 1 | Micafungin |
|--------------------------------|------------|
| Started                        | 35         |
| Treated                        | 35         |
| Completed                      | 20         |
| Not completed                  | 15         |
| Death                          | 3          |
| Miscellaneous                  | 4          |
| Infection not confirmed        | 4          |
| Lack of efficacy               | 4          |



## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Micafungin |
|-----------------------|------------|

Reporting group description:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour. Micafungin was administered for a minimum of 14 days until 1 of the following conditions applied:

- Negative results (absence of Candida growth) from at least 2 consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level (< 125 pg/mL) were obtained.
- In case of meningitis, hydrocephalus and external ventricular derivation, negative results (absence of Candida growth) from at least 2 consecutive cerebral spinal fluid (CSF) cultures associated with resolution of clinical and laboratory symptoms.
- Interruption (including addition or switch to another antifungal agent or dosage change of micafungin) due to demonstration of therapy failure.

| Reporting group values   | Micafungin     | Total |  |
|--|----------------|-------|--|
| Number of subjects   | 35             | 35    |  |
| Age categorical<br>Units: Subjects                                       |                |       |  |
| Age continuous<br>Units: months<br>arithmetic mean<br>standard deviation | 2.53<br>± 2.11 | -     |  |
| Gender categorical<br>Units:   |                |       |  |
| Male   | 20             | 20    |  |
| Female   | 15             | 15    |  |
| Race<br>Units: Subjects  |                |       |  |
| Caucasian  | 32             | 32    |  |
| Black  | 2              | 2     |  |
| Other  | 1              | 1     |  |

## End points

### End points reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Micafungin |
|-----------------------|------------|

Reporting group description:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour. Micafungin was administered for a minimum of 14 days until 1 of the following conditions applied:

- Negative results (absence of Candida growth) from at least 2 consecutive blood cultures and/or resolution of clinical and laboratory symptoms and reduction of mannan antigen blood level (< 125 pg/mL) were obtained.
- In case of meningitis, hydrocephalus and external ventricular derivation, negative results (absence of Candida growth) from at least 2 consecutive cerebral spinal fluid (CSF) cultures associated with resolution of clinical and laboratory symptoms.
- Interruption (including addition or switch to another antifungal agent or dosage change of micafungin) due to demonstration of therapy failure.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Safety Analysis Set (SAF) |
|----------------------------|---------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The SAF consisted of all enrolled (intent to treat [ITT]) participants who had received at least 1 dose of study drug.

### Primary: Concentration of Micafungin in Blood

|                 |   |
|-----------------|---|
| End point title | Concentration of Micafungin in Blood <sup>[1]</sup> |
|-----------------|---|

End point description:

Concentration was determined from the PK blood samples collected via capillary micro-method (draws from the heel). The analysis population consisted of the pharmacokinetic analysis set (PKAS) which was defined as a subset of the SAF who had at least one blood draw.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose and after 1, 3, and 8 hours post-dose on one of treatment days from Day 3 to Day 10

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: All variables were presented using descriptive statistics only.

| End point values                     | Micafungin       |  |  |  |
|--------------------------------------|------------------|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 34               |  |  |  |
| Units: mcg/mL                        |                  |  |  |  |
| arithmetic mean (standard deviation) |                  |  |  |  |
| Pre-dose                             | 5.702 (± 2.685)  |  |  |  |
| 1 hour post-dose                     | 17.233 (± 6.296) |  |  |  |
| 3 hours post-dose                    | 15.591 (± 5.988) |  |  |  |
| 8 hours post-dose                    | 10.273 (± 3.346) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Primary: Concentration of Micafungin in CSF

|   |   |
|---|---|
| End point title   | Concentration of Micafungin in CSF <sup>[2]</sup> |
| End point description:<br>Concentration was to be determined from the CSF samples collected. The analysis population consisted of the SAF (only participants that had CSF samples collected). Data for concentration of micafungin in CSF was not evaluable due to insufficient number of participants with CSF samples collected. Data not evaluable denoted as "99999." |   |
| End point type  | Primary   |
| End point timeframe:<br>Predose and after 1, 3, and 8 hours post-dose on one of treatment days from Day 3 to Day 10   |   |

Notes:

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

Justification: All variables were presented using descriptive statistics only.

| End point values                     | Micafungin      |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 1               |  |  |  |
| Units: mg/mL                         |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Pre-dose                             | 99999 (± 99999) |  |  |  |
| 1 hour post-dose                     | 99999 (± 99999) |  |  |  |
| 3 hours post-dose                    | 99999 (± 99999) |  |  |  |
| 8 hours post-dose                    | 99999 (± 99999) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with A Response at End of Treatment (EOT) - Success of Therapy (SOT)

|  |   |
|--|---|
| End point title  | Percentage of Participants with A Response at End of Treatment (EOT) - Success of Therapy (SOT) |
| End point description:<br>For systemic candidiasis (SC) participants, SOT was determined by survival associated with negative Candida test results of 2 consecutive blood cultures, completed at start of treatment, or resolution of clinical & laboratory symptoms together with reduction of mannan antigen blood level (MABL) (<125 pg/ml). For Candida meningitis (CM), SOT was determined by survival associated with negative Candida test results of at least 2 consecutive CSF cultures, completed at start of treatment and resolution of clinical & lab symptoms. For hydrocephalus due to Candida infection (CI) and/or external ventricular derivation (EVD), SOT was determined by survival associated with negative Candida test results of at least 2 consecutive CSF cultures, completed at start of treatment. The analysis population consisted of the SAF (only participants that completed 14 days of treatment), 20 participants completed treatment and 16 had SOT. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Up to day 14   |   |



|                                   |                     |  |  |  |
|-----------------------------------|---------------------|--|--|--|
| <b>End point values</b>           | Micafungin          |  |  |  |
| Subject group type                | Reporting group     |  |  |  |
| Number of subjects analysed       | 16                  |  |  |  |
| Units: percentage of participants |                     |  |  |  |
| number (confidence interval 95%)  |                     |  |  |  |
| Success                           | 80 (56.34 to 94.27) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with A Response at EOT - Failure of Therapy (FOT)

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with A Response at EOT - Failure of Therapy (FOT) |
|-----------------|--|

End point description:

For SC participants, FOT was determined by death due to Candida sepsis, by confirmation of persistence of positive Candida test results from 1 blood culture completed by need to add/switch to another antifungal agent (AA) and/or change of micafungin dose for resolution of infection at any time or by the persistence of Candida colonization in different indicated sites associated with persistence of clinical & lab symptoms & with high (MABL) ( $\geq 125$  pg/ml). For CM, FOT was determined by death due to CM, by persistence of CI from confirmation of positive CSF culture or by need to add/switch to another AA or dose change of micafungin for resolution of CI at any time. For hydrocephalus due to CI and/or EVD, FOT was determined by death due to CI, by need to add/switch to another AA or dose change of micafungin for resolution of CI at any time or by persistence of CI as from confirmation of positive CSF culture. SAF (those that completed 14 days of treatment (20)), 4 had FOT.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to day 14

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | Micafungin      |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 4               |  |  |  |
| Units: percentage of participants |                 |  |  |  |
| number (not applicable)           |                 |  |  |  |
| Failure                           | 20              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adverse Events (AEs)

|   |  |
|---|--|
| End point title   | Number of Participants with Adverse Events (AEs) |
| End point description:  |  |
| An adverse event (AE) was defined as any untoward medical occurrence in a participant administered a study drug or who had undergone study procedures which did not necessarily have a causal relationship with this treatment. This included abnormal laboratory tests, vital signs, electrocardiogram data or physical examinations that were defined as AEs if the abnormality induced clinical signs or symptoms, required active intervention, interruption or discontinuation of study drug or was clinically significant in the investigator's opinion. The following standard with 3 grades was used to measure the severity of AEs, including abnormal clinical laboratory values: • Mild: No disruption of normal daily activities • Moderate: Affected normal daily activities • Severe: Inability to perform daily activities. A treatment-emergent adverse event (TEAE) was defined as an AE observed after starting administration of the test drug/comparative drug. The analysis population consisted of the SAF. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| From the first dose of study drug administration up 72 hours after the last dose, up to 17 days.  |  |

| End point values                                   | Micafungin      |  |  |  |
|--|-----------------|--|--|--|
| Subject group type                                 | Reporting group |  |  |  |
| Number of subjects analysed                        | 35              |  |  |  |
| Units: participants                                |                 |  |  |  |
| Any TEAE   | 31              |  |  |  |
| Drug-related TEAEs                                 | 1               |  |  |  |
| TEAE with Unknown Relationship to Study Drug       | 15              |  |  |  |
| Serious TEAEs                                      | 12              |  |  |  |
| Drug-related Serious TEAEs                         | 0               |  |  |  |
| Serious TEAEs with Unk. Relationship to Study Drug | 3               |  |  |  |
| TEAEs Leading to Death                             | 3               |  |  |  |
| Drug-related TEAEs Leading to Death                | 0               |  |  |  |
| TEAEs Leading to Death - Unk. Rel. to Study Drug   | 0               |  |  |  |
| TEAEs Leading to Withdrawal of Treatment (Tx)      | 0               |  |  |  |
| Drug-Related TEAE Leading to Withdrawal of Tx      | 0               |  |  |  |
| TEAE Leading to Wdl. of Tx Unk. Rel. to Study Drug | 0               |  |  |  |
| Death  | 5               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Comparison of Capillary and Venous Plasma Concentrations of Micafungin

|  |  |
|--|--|
| End point title  | Comparison of Capillary and Venous Plasma Concentrations of Micafungin |
| End point description:   |  |
| Micafungin concentrations were determined from the PK blood samples collected via both capillary micro-method (draws from the heel) and venous methods. The analysis population consisted of the SAF |  |

(only participants where blood was withdrawn by both capillary and venous methods), 8 participants had blood withdrawn by both methods. N = number of participants.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Predose and after 1, 3, and 8 hours post-dose on one of treatment days from Day 3 to Day 10

| End point values                     | Micafungin       |  |  |  |
|--------------------------------------|------------------|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 8 <sup>[3]</sup> |  |  |  |
| Units: mcg/mL                        |                  |  |  |  |
| arithmetic mean (standard deviation) |                  |  |  |  |
| Capillary - Pre-dose                 | 6.179 (± 2.864)  |  |  |  |
| Capillary - 1 hour post-dose         | 19.196 (± 5.659) |  |  |  |
| Capillary - 3 hours post-dose        | 16.935 (± 4.075) |  |  |  |
| Capillary - 8 hours post-dose        | 11.834 (± 2.433) |  |  |  |
| Venous - Pre-dose                    | 6.431 (± 2.841)  |  |  |  |
| Venous - 1 hour post-dose            | 22.390 (± 4.972) |  |  |  |
| Venous - 3 hours post-dose           | 19.000 (± 3.945) |  |  |  |
| Venous - 8 hours post-dose           | 12.994 (± 2.765) |  |  |  |

Notes:

[3] - For venous 1, 3 and 8 hours post-dose, n=7.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug administration up 72 hours after the last dose, up to 17 days.

Adverse event reporting additional description:

The total number of deaths (all causes) includes deaths reported after the time frame above.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Micafungin |
|-----------------------|------------|

Reporting group description:

Participants received micafungin 8 mg/kg per day via intravenous infusion for approximately 1 hour.

| Serious adverse events                            | Micafungin       |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 12 / 35 (34.29%) |  |  |
| number of deaths (all causes)                     | 5                |  |  |
| number of deaths resulting from adverse events    | 3                |  |  |
| Vascular disorders                                |                  |  |  |
| Hypotension                                       |                  |  |  |
| subjects affected / exposed                       | 1 / 35 (2.86%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Cardiac disorders                                 |                  |  |  |
| Bradycardia                                       |                  |  |  |
| subjects affected / exposed                       | 2 / 35 (5.71%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 2            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Blood and lymphatic system disorders              |                  |  |  |
| Neutropenia                                       |                  |  |  |
| subjects affected / exposed                       | 1 / 35 (2.86%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Gastrointestinal disorders                        |                  |  |  |
| Ascites   |                  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Pulmonary hypertension                          |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory failure                             |                |  |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Acute kidney injury                             |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Anuria  |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bacterial sepsis                                |                |  |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Candida sepsis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 35 (2.86%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Klebsiella sepsis                               |                |  |  |
| subjects affected / exposed                     | 2 / 35 (5.71%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Septic shock                                    |                |  |  |
| subjects affected / exposed                     | 3 / 35 (8.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 3          |  |  |

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

| <b>Non-serious adverse events</b>                     | Micafungin       |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 25 / 35 (71.43%) |  |  |
| Investigations  |                  |  |  |
| Blood alkaline phosphatase increased                  |                  |  |  |
| subjects affected / exposed                           | 2 / 35 (5.71%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Blood bilirubin increased                             |                  |  |  |
| subjects affected / exposed                           | 2 / 35 (5.71%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| C-reactive protein increased                          |                  |  |  |
| subjects affected / exposed                           | 2 / 35 (5.71%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Gamma-glutamyltransferase increased                   |                  |  |  |
| subjects affected / exposed                           | 9 / 35 (25.71%)  |  |  |
| occurrences (all)                                     | 11               |  |  |
| Injury, poisoning and procedural complications        |                  |  |  |
| Wound dehiscence                                      |                  |  |  |
| subjects affected / exposed                           | 2 / 35 (5.71%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Vascular disorders                                    |                  |  |  |
| Hypotension   |                  |  |  |
| subjects affected / exposed                           | 2 / 35 (5.71%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Cardiac disorders                                     |                  |  |  |
| Bradycardia   |                  |  |  |
| subjects affected / exposed                           | 2 / 35 (5.71%)   |  |  |
| occurrences (all)                                     | 2                |  |  |
| Blood and lymphatic system disorders                  |                  |  |  |

|  |  |  |  |
|--|--|--|--|
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 35 (5.71%)<br>2                            |  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 35 (8.57%)<br>3                            |  |  |
| General disorders and administration site conditions<br>Oedema<br>subjects affected / exposed<br>occurrences (all)   | 5 / 35 (14.29%)<br>5                           |  |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 35 (5.71%)<br>2                            |  |  |
| Hepatobiliary disorders<br>Cholestasis<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypertransaminasaemia<br>subjects affected / exposed<br>occurrences (all)            | 3 / 35 (8.57%)<br>3<br><br>2 / 35 (5.71%)<br>2 |  |  |
| Infections and infestations<br>Sepsis<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection bacterial<br>subjects affected / exposed<br>occurrences (all) | 2 / 35 (5.71%)<br>2<br><br>2 / 35 (5.71%)<br>2 |  |  |
| Metabolism and nutrition disorders<br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)        | 2 / 35 (5.71%)<br>2<br><br>3 / 35 (8.57%)<br>3 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 25 May 2015       | <p>The changes include:</p> <ul style="list-style-type: none"><li>• Changed the cutoff for positive mannan antigen test results from 250 to 125 pg/mL</li><li>• Specified that absence of Candida growth in case of Candida meningitis, hydrocephalus due to Candida infection and/or external ventricular derivation could be based on negative results from 2 instead of 3 consecutive CSF cultures</li><li>• Changed the age of patients to be enrolled from 90 to 180 days and specified the age calculation based on gestational age.</li><li>• Specified that at least 4 neonates with Candida meningitis, hydrocephalus due to Candida infection and/or external ventricular derivation were to be enrolled</li><li>• Updated the exclusion criteria</li><li>• Allowed patient to start study drug administration as soon as possible after screening rather than the day of screening</li><li>• Added anthropometric parameters at birth as a screening/baseline evaluation</li></ul> |
| 13 September 2017 | <p>The changes include:</p> <ul style="list-style-type: none"><li>• Updated contact information of sponsor and contract research organization</li><li>• Clarified that neonates with Candida meningitis, hydrocephalus due to Candida infection and/or external ventricular derivation would only be included if available during the enrollment period</li><li>• Added in vitro susceptibility testing of the collected Candida spp isolates to determine the MIC for micafungin</li><li>• Extended the trial end date</li><li>• Updated the information on labeling of primary and secondary packages and syringes</li><li>• Updated the information on the reporting of SAEs</li></ul>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Participants were re-consented under Astellas sponsorship, the last informed consent (ICF) was collected on 10APR2018, this is considered the global end of trial date.

Notes: