



## Clinical trial results:

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

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-005030-54 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 31 July 2006   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 10 February 2016 |
| First version publication date | 15 July 2015     |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | MK-0991-042 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00292071 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                              |
|------------------------------|----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Merck Sharp & Dohme Corp.                                                                    |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033                               |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<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? | Yes                 |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |

Notes:

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**Results analysis stage**

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

Notes:

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**General information about the trial**

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Main objective of the trial:

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

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

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

Background therapy: -

Evidence for comparator: -

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

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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

Notes:

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**Subjects enrolled per age group**

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

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

## Subject disposition

### Recruitment

Recruitment details:

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

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|           |                                       |
|-----------|---------------------------------------|
| Arm title | Caspofungin 50 mg/m <sup>2</sup> /day |
|-----------|---------------------------------------|

Arm description:

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

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Caspofungin           |
| Investigational medicinal product code |                       |
| Other name                             | CANCIDAS™, MK-0991    |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Caspofungin acetate 50 mg/m<sup>2</sup>/day in a 1-hour intravenous infusion for a minimum of 4 days and a maximum of 28 days. Infusion employed a pediatric syringe or ambulatory pump.

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

## Baseline characteristics

### Reporting groups

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Caspofungin 50 mg/m <sup>2</sup> /day |
|-----------------------|---------------------------------------|

Reporting group description:

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

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

## End points

### End points reporting groups

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

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

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Area Under the Plasma Concentration Curve of Caspofungin up to 24 Hours (AUC0-24) on Day 1 <sup>[1]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

Notes:

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

### Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Plasma Concentration of Caspofungin at One Hour (C1hr) on Day 1 |
|-----------------|-----------------------------------------------------------------|

End point description:

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

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

End point timeframe:

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

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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Notes:

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

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

Notes:

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

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

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

Notes:

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

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

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

### Statistical analyses

No statistical analyses for this end point

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

|                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                 | Percentage of Participants with One or More Adverse Events |
| End point description:<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 study drug, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the product, is also an adverse experience. |                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary                                                  |
| End point timeframe:<br>Up to 14 days after the last dose of study drug                                                                                                                                                                                                                                                                                                                                         |                                                            |

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                 |
|-----------------|-----------------------------------------------------------------|
| End point title | Percentage of Participants Discontinued Due to an Adverse Event |
|-----------------|-----------------------------------------------------------------|

End point description:

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drug, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the product, is also an adverse experience.

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

End point timeframe:

Up to 14 days after the last dose of study drug

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 14 days after the last dose of study drug

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

### Reporting groups

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Caspofungin 50 mg/m <sup>2</sup> /day |
|-----------------------|---------------------------------------|

Reporting group description:

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

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

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

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

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

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

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

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

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| Metabolism and nutrition disorders |                |  |  |
| Metabolic acidosis                 |                |  |  |
| subjects affected / exposed        | 1 / 9 (11.11%) |  |  |
| occurrences (all)                  | 1              |  |  |

## **More information**

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

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported