



## Clinical trial results:

### A PROSPECTIVE, OPEN-LABEL, NON-COMPARATIVE STUDY TO ASSESS THE SAFETY, TOLERABILITY AND EFFICACY OF VORICONAZOLE FOR THE PRIMARY AND SALVAGE TREATMENT OF INVASIVE CANDIDIASIS, CANDIDEMIA, AND ESOPHAGEAL CANDIDIASIS IN PEDIATRIC SUBJECTS

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2009-012848-16                   |
| Trial protocol           | DE HU SK CZ BG RO Outside EU/EEA |
| Global end of trial date | 08 July 2013                     |

#### Results information

|                                |  |
|--------------------------------|--|
| Result version number          | v2 (current)   |
| This version publication date  | 02 June 2016   |
| First version publication date | 01 August 2015   |
| Version creation reason        | • Correction of full data set<br>Reporting periods and duplicate Adverse Events in their data. |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A1501085 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01092832 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Pfizer Inc.   |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017  |
| Public contact               | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact           | Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 12 August 2014 |
| Is this the analysis of the primary completion data? | No             |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 08 July 2013 |
| Was the trial ended prematurely? | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and tolerability of voriconazole for the treatment of invasive candidiasis, including candidemia, and esophageal candidiasis in pediatric subjects 2 to less than (<)18 years of age.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 28 October 2010 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Poland: 1         |
| Country: Number of subjects enrolled | Slovakia: 1       |
| Country: Number of subjects enrolled | Czech Republic: 7 |
| Country: Number of subjects enrolled | Hungary: 2        |
| Country: Number of subjects enrolled | Mexico: 5         |
| Country: Number of subjects enrolled | Philippines: 1    |
| Country: Number of subjects enrolled | China: 2          |
| Country: Number of subjects enrolled | Hong Kong: 3      |
| Worldwide total number of subjects   | 22                |
| EEA total number of subjects         | 11                |

Notes:

### Subjects enrolled per age group

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

|                           |    |
|---------------------------|----|
| Children (2-11 years)     | 14 |
| Adolescents (12-17 years) | 8  |
| Adults (18-64 years)      | 0  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Total 22 subjects were treated from 11 centers across 8 countries. 21 subjects completed the study and 1 subject discontinued from the study, reason not specified.

### Period 1

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

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes                          |
| <b>Arm title</b>             | Voriconazole: 2 to <12 years |

Arm description:

Subjects aged 2 to <12 years with invasive candidiasis/candidemia (ICC) received a loading dose of voriconazole, every 12 hours (q12h) for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 5 days. Subjects with esophageal candidiasis (EC) received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to oral (PO) therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment.

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

Dosage and administration details:

Subjects with ICC received a loading dose of voriconazole 9 milligram per kilogram (mg/kg), intravenously (IV), q12h for the first 24 hours, followed by maintenance dosing of voriconazole 8 mg/kg, IV, q12h for a minimum of 5 days of IV therapy. Subjects with EC received voriconazole 4 mg/kg, IV, q12h for a minimum of 5 days of IV therapy.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | Voriconazole                       |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Powder for oral suspension, Tablet |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects in both ICC and EC, once signs and symptoms of Candida infection had resolved and was clinically stable received voriconazole (either oral suspension or tablets) 9 mg/kg, q12h (maximum dose of 350 mg).

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Voriconazole: 12 to <18 years |
|------------------|-------------------------------|

Arm description:

Subjects aged 12 to <18 years (excluding those aged 12-14 years weighing <50 kg) with ICC received a loading dose of voriconazole, q12h for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 7 days. Subjects with EC received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to PO therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Voriconazole                     |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Subjects with ICC received a loading dose of voriconazole 6 mg/kg, IV, q12h for the first 24 hours, followed by maintenance dosing of voriconazole 4 mg/kg, IV, q12h for a minimum of 7 days of IV therapy. Subjects with EC received voriconazole 3 mg/kg, IV, q12h for a minimum of 5 days of IV therapy.

|  |                                    |
|--|------------------------------------|
| Investigational medicinal product name | Voriconazole                       |
| Investigational medicinal product code |                                    |
| Other name                             |                                    |
| Pharmaceutical forms                   | Powder for oral suspension, Tablet |
| Routes of administration               | Oral use                           |

Dosage and administration details:

Subjects in both ICC and EC, once signs and symptoms of Candida infection had resolved and was clinically stable received voriconazole (either oral suspension or tablets) 200 mg, q12h.

| <b>Number of subjects in period 1</b> | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years |
|---------------------------------------|------------------------------|-------------------------------|
| Started                               | 14                           | 8                             |
| Completed                             | 13                           | 8                             |
| Not completed                         | 1                            | 0                             |
| Not specified                         | 1                            | -                             |

## Baseline characteristics

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Voriconazole: 2 to <12 years |
|-----------------------|------------------------------|

Reporting group description:

Subjects aged 2 to <12 years with invasive candidiasis/candidemia (ICC) received a loading dose of voriconazole, every 12 hours (q12h) for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 5 days. Subjects with esophageal candidiasis (EC) received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to oral (PO) therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Voriconazole: 12 to <18 years |
|-----------------------|-------------------------------|

Reporting group description:

Subjects aged 12 to <18 years (excluding those aged 12-14 years weighing <50 kg) with ICC received a loading dose of voriconazole, q12h for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 7 days. Subjects with EC received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to PO therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment.

| Reporting group values             | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years | Total |
|------------------------------------|------------------------------|-------------------------------|-------|
| Number of subjects                 | 14                           | 8                             | 22    |
| Age categorical<br>Units: Subjects |                              |                               |       |

|   |              |               |    |
|---|--------------|---------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 6.8<br>± 2.9 | 14.4<br>± 1.7 | -  |
| Gender categorical<br>Units: Subjects                                   |              |               |    |
| Female  | 8            | 6             | 14 |
| Male  | 6            | 2             | 8  |

## End points

### End points reporting groups

|  |                               |
|--|-------------------------------|
| Reporting group title  | Voriconazole: 2 to <12 years  |
| Reporting group description:<br>Subjects aged 2 to <12 years with invasive candidiasis/candidemia (ICC) received a loading dose of voriconazole, every 12 hours (q12h) for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 5 days. Subjects with esophageal candidiasis (EC) received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to oral (PO) therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment. |                               |
| Reporting group title  | Voriconazole: 12 to <18 years |
| Reporting group description:<br>Subjects aged 12 to <18 years (excluding those aged 12-14 years weighing <50 kg) with ICC received a loading dose of voriconazole, q12h for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 7 days. Subjects with EC received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to PO therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment.                                |                               |

### Primary: Percentage of Subjects With Adverse Events - Overall Summary

|   |   |
|---|---|
| End point title   | Percentage of Subjects With Adverse Events - Overall Summary <sup>[1]</sup> |
| End point description:<br>Percentage of subjects with adverse events (AEs), serious adverse events (SAEs), severe AEs, who discontinued due to AEs, or who had dose reduced or temporarily discontinued due to AEs. Safety population.                                    |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline up to 1 month follow-up  |   |
| Notes:<br>[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.<br>Justification: Only descriptive statistics was planned to be reported for this endpoint. |   |

| End point values                                 | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years |  |  |
|--|------------------------------|-------------------------------|--|--|
| Subject group type                               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed                      | 14                           | 8                             |  |  |
| Units: percentage of subjects                    |                              |                               |  |  |
| number (not applicable)                          |                              |                               |  |  |
| With AEs   | 92.9                         | 75                            |  |  |
| With SAEs  | 14.3                         | 12.5                          |  |  |
| With severe AEs                                  | 28.6                         | 37.5                          |  |  |
| Discontinued due to AEs                          | 14.3                         | 25                            |  |  |
| Dose reduced/temporary discontinuation due to AE | 21.4                         | 0                             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With a Global Response of Success at End of Treatment (EOT)

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With a Global Response of Success at End of Treatment (EOT) |
|-----------------|--|

End point description:

Global response was determined programmatically based on investigator assessment of clinical and microbiological response. Global response of success was defined as clinical cure or improvement and microbiological eradication or presumed eradication. Exact 95 percent (%) confidence interval for binomial proportions using Clopper-Pearson method. Modified Intent-to-Treat (MITT) Population: all subjects who received at least 1 dose of study medication and who have confirmed ICC, EC or subjects with EC who do not have confirmation of EC by esophagoscopy, but who had at least confirmation of oropharyngeal candidiasis.

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

End point timeframe:

EOT (upto Day 42)

| End point values                 | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years |  |  |
|----------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed      | 9                            | 8                             |  |  |
| Units: percentage of subjects    |                              |                               |  |  |
| number (confidence interval 95%) | 88.9 (51.75 to 99.72)        | 62.5 (24.49 to 91.48)         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: All-Cause Mortality - Number of Subject Deaths

|                 |  |
|-----------------|--|
| End point title | All-Cause Mortality - Number of Subject Deaths |
|-----------------|--|

End point description:

Safety population.

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

End point timeframe:

Day 28 and 1 Month Follow-up

| End point values            | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years |  |  |
|-----------------------------|------------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed | 14                           | 8                             |  |  |
| Units: subjects             |                              |                               |  |  |
| number (not applicable)     |                              |                               |  |  |
| Day 28                      | 0                            | 0                             |  |  |
| 1 Month Follow-up           | 0                            | 0                             |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Death

|   |               |
|---|---------------|
| End point title   | Time to Death |
| End point description:<br>No subject died within the safety reporting period, therefore time to death was not applicable. |               |
| End point type  | Secondary     |
| End point timeframe:<br>Baseline up to 1 month follow-up  |               |

| End point values              | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years |  |  |
|-------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type            | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed   | 0 <sup>[2]</sup>             | 0 <sup>[3]</sup>              |  |  |
| Units: months                 |                              |                               |  |  |
| median (full range (min-max)) | ( to )                       | ( to )                        |  |  |

Notes:

[2] - No subject died within the safety reporting period.

[3] - No subject died within the safety reporting period.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 49 (7 days after the last dose of study drug)

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Voriconazole: 2 to <12 years |
|-----------------------|------------------------------|

Reporting group description:

Subjects aged 2 to <12 years with invasive candidiasis/candidemia (ICC) received a loading dose of voriconazole, every 12 hours (q12h) for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 5 days. Subjects with esophageal candidiasis (EC) received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to oral (PO) therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Voriconazole: 12 to <18 years |
|-----------------------|-------------------------------|

Reporting group description:

Subjects aged 12 to <18 years (excluding those aged 12-14 years weighing <50 kg) with ICC received a loading dose of voriconazole, q12h for the first 24 hours, followed by maintenance dose of voriconazole, q12h for a minimum of 7 days. Subjects with EC received voriconazole, q12h for a minimum of 5 days. In both ICC and EC, once signs and symptoms of Candida infection had resolved and the subject was clinically stable, subjects were switched to PO therapy and received voriconazole, q12h. Voriconazole was administered for at least 7 days (subjects with EC) or 14 days (subjects with ICC) after last positive blood culture up to a maximum of 42 days of treatment.

| Serious adverse events                            | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years |  |
|---|------------------------------|-------------------------------|--|
| Total subjects affected by serious adverse events |                              |                               |  |
| subjects affected / exposed                       | 2 / 14 (14.29%)              | 1 / 8 (12.50%)                |  |
| number of deaths (all causes)                     | 1                            | 0                             |  |
| number of deaths resulting from adverse events    |                              |                               |  |
| Injury, poisoning and procedural complications    |                              |                               |  |
| Pneumonia   |                              |                               |  |
| subjects affected / exposed                       | 1 / 14 (7.14%)               | 0 / 8 (0.00%)                 |  |
| occurrences causally related to treatment / all   | 0 / 1                        | 0 / 0                         |  |
| deaths causally related to treatment / all        | 0 / 0                        | 0 / 0                         |  |
| Blood and lymphatic system disorders              |                              |                               |  |
| Febrile neutropenia                               |                              |                               |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 14 (7.14%) | 0 / 8 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Splenic candidiasis                             |                |                |  |
| subjects affected / exposed                     | 0 / 14 (0.00%) | 1 / 8 (12.50%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Voriconazole: 2 to <12 years | Voriconazole: 12 to <18 years |  |
|---|------------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events |                              |                               |  |
| subjects affected / exposed                           | 13 / 14 (92.86%)             | 6 / 8 (75.00%)                |  |
| Vascular disorders                                    |                              |                               |  |
| Hypertension  |                              |                               |  |
| subjects affected / exposed                           | 2 / 14 (14.29%)              | 0 / 8 (0.00%)                 |  |
| occurrences (all)                                     | 3                            | 0                             |  |
| Phlebitis   |                              |                               |  |
| subjects affected / exposed                           | 0 / 14 (0.00%)               | 1 / 8 (12.50%)                |  |
| occurrences (all)                                     | 0                            | 1                             |  |
| Venoocclusive disease                                 |                              |                               |  |
| subjects affected / exposed                           | 1 / 14 (7.14%)               | 0 / 8 (0.00%)                 |  |
| occurrences (all)                                     | 1                            | 0                             |  |
| General disorders and administration site conditions  |                              |                               |  |
| Device occlusion                                      |                              |                               |  |
| subjects affected / exposed                           | 0 / 14 (0.00%)               | 1 / 8 (12.50%)                |  |
| occurrences (all)                                     | 0                            | 1                             |  |
| Hypothermia   |                              |                               |  |
| subjects affected / exposed                           | 2 / 14 (14.29%)              | 1 / 8 (12.50%)                |  |
| occurrences (all)                                     | 3                            | 2                             |  |
| Pyrexia   |                              |                               |  |
| subjects affected / exposed                           | 2 / 14 (14.29%)              | 1 / 8 (12.50%)                |  |
| occurrences (all)                                     | 2                            | 1                             |  |
| Reproductive system and breast disorders              |                              |                               |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Testicular mass<br>subjects affected / exposed<br>occurrences (all)      | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders                          |                     |                     |  |
| Atelectasis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Bronchospasm<br>subjects affected / exposed<br>occurrences (all)         | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Hydrothorax<br>subjects affected / exposed<br>occurrences (all)          | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Hypoventilation<br>subjects affected / exposed<br>occurrences (all)      | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Pharyngeal erythema<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Pneumothorax<br>subjects affected / exposed<br>occurrences (all)         | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Respiratory disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)            | 1 / 14 (7.14%)<br>2 | 0 / 8 (0.00%)<br>0  |  |
| Investigations   |                     |                     |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| Alanine aminotransferase abnormal<br>subjects affected / exposed   | 3 / 14 (21.43%) | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 3               | 0              |  |
| Alanine aminotransferase increased<br>subjects affected / exposed  | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 2               | 0              |  |
| Aspartate aminotransferase<br>abnormal                             |                 |                |  |
| subjects affected / exposed  | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 1               | 0              |  |
| Aspartate aminotransferase<br>increased                            |                 |                |  |
| subjects affected / exposed  | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 2               | 0              |  |
| Blood alkaline phosphatase abnormal<br>subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 1               | 0              |  |
| Blood triglycerides increased<br>subjects affected / exposed       | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)  | 0               | 1              |  |
| Drug level decreased<br>subjects affected / exposed                | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)  | 0               | 1              |  |
| Gamma-glutamyltransferase<br>abnormal                              |                 |                |  |
| subjects affected / exposed  | 2 / 14 (14.29%) | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 2               | 0              |  |
| Gamma-glutamyltransferase<br>increased                             |                 |                |  |
| subjects affected / exposed  | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)  | 0               | 1              |  |
| Haematocrit abnormal<br>subjects affected / exposed                | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 2               | 0              |  |
| Hepatic enzyme increased<br>subjects affected / exposed            | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)  | 1               | 0              |  |
| Lymphocyte percentage abnormal                                     |                 |                |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Monocyte count abnormal<br>subjects affected / exposed<br>occurrences (all)                | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Staphylococcus test positive<br>subjects affected / exposed<br>occurrences (all)           | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Injury, poisoning and procedural complications   |                     |                     |  |
| Drug dose omission<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Incision site pain<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Incorrect drug administration rate<br>subjects affected / exposed<br>occurrences (all)     | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Refractoriness to platelet transfusion<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Transplant failure<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Underdose<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Cardiac disorders  |                     |                     |  |
| Pericardial effusion<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Nervous system disorders   |                     |                     |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)      | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Blood and lymphatic system disorders                                  |                     |                     |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 14 (7.14%)<br>3 | 0 / 8 (0.00%)<br>0  |  |
| Hypothrombinaemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Leukocytosis<br>subjects affected / exposed<br>occurrences (all)      | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 14 (7.14%)<br>2 | 0 / 8 (0.00%)<br>0  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)       | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Platelet disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1 | 1 / 8 (12.50%)<br>1 |  |
| Ear and labyrinth disorders   |                     |                     |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)           | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>2 |  |
| Eye disorders   |                     |                     |  |
| Amaurosis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)    | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Corneal opacity   |                     |                     |  |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Eye pruritus                |                 |                |  |
| subjects affected / exposed | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)           | 0               | 1              |  |
| Eyelid disorder             |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Photophobia                 |                 |                |  |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 8 (12.50%) |  |
| occurrences (all)           | 2               | 2              |  |
| Retinal disorder            |                 |                |  |
| subjects affected / exposed | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)           | 0               | 1              |  |
| Visual acuity reduced       |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Gastrointestinal disorders  |                 |                |  |
| Abdominal pain              |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Ascites                     |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Constipation                |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 1 / 8 (12.50%) |  |
| occurrences (all)           | 1               | 1              |  |
| Nausea                      |                 |                |  |
| subjects affected / exposed | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)           | 0               | 1              |  |
| Oesophagitis                |                 |                |  |
| subjects affected / exposed | 0 / 14 (0.00%)  | 2 / 8 (25.00%) |  |
| occurrences (all)           | 0               | 2              |  |
| Tongue ulceration           |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 1 / 14 (7.14%)<br>1  | 1 / 8 (12.50%)<br>1 |  |
| Hepatobiliary disorders  |                      |                     |  |
| Gallbladder disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Hepatosplenomegaly<br>subjects affected / exposed<br>occurrences (all)   | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Jaundice<br>subjects affected / exposed<br>occurrences (all)             | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Liver disorder<br>subjects affected / exposed<br>occurrences (all)       | 1 / 14 (7.14%)<br>2  | 0 / 8 (0.00%)<br>0  |  |
| Skin and subcutaneous tissue disorders                                   |                      |                     |  |
| Dermatitis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Dermatosis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Purpura<br>subjects affected / exposed<br>occurrences (all)              | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 14 (21.43%)<br>3 | 0 / 8 (0.00%)<br>0  |  |
| Scab<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 14 (7.14%)<br>1  | 0 / 8 (0.00%)<br>0  |  |
| Renal and urinary disorders  |                      |                     |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Cystitis haemorrhagic<br>subjects affected / exposed<br>occurrences (all)   | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Infections and infestations<br>Anorectal cellulitis<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Bone abscess<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Bronchopulmonary aspergillosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)   | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 14 (7.14%)<br>1 | 0 / 8 (0.00%)<br>0  |  |
| Splenic candidiasis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 14 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |  |
| Metabolism and nutrition disorders<br>Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 14 (7.14%)<br>1 | 1 / 8 (12.50%)<br>1 |  |

|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| Hyperkalaemia               |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Hypermagnesaemia            |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Hypertriglyceridaemia       |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Hypoalbuminaemia            |                 |                |  |
| subjects affected / exposed | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)           | 0               | 1              |  |
| Hypocalcaemia               |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Hypochloraemia              |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Hypoglycaemia               |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Hypokalaemia                |                 |                |  |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 4               | 0              |  |
| Hyponatraemia               |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 0 / 8 (0.00%)  |  |
| occurrences (all)           | 1               | 0              |  |
| Hypophagia                  |                 |                |  |
| subjects affected / exposed | 0 / 14 (0.00%)  | 1 / 8 (12.50%) |  |
| occurrences (all)           | 0               | 1              |  |
| Hypophosphataemia           |                 |                |  |
| subjects affected / exposed | 1 / 14 (7.14%)  | 1 / 8 (12.50%) |  |
| occurrences (all)           | 2               | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 24 November 2009 | <p>The primary reason for creation of this protocol amendment was to include additional visual safety assessments, as requested by the United States Food and Drug Administration (FDA).</p> <p>1- Dilated fundoscopic examination at the EOT and at the 1-month follow-up visit. These assessments were in addition to the dilated fundoscopic examination already required at the time of Screening.</p> <p>2- Confrontational and/or automated visual field test at the time of Screening and at the EOT in subjects 5 years of age and older. For subjects who were critically ill and/or clinically unstable at Baseline, visual field testing could be performed at a later time, when, in the investigator's judgment, the subject was clinically stable and able to perform the test adequately.</p> <p>3- In subjects 3 years of age and younger, visual safety monitoring was limited to visual acuity and dilated fundoscopy. In children who were too young to perform the visual acuity test, fixation should have been assessed as to whether it is central, steady or maintained in each eye.</p> <p>4- Assessment of vital signs, and signs and symptoms of Candida infection (including radiologic findings) every 3 days was no longer required in subjects who have been discharged from the hospital and are continuing to receive study drug treatment on an outpatient basis.</p> <p>5- In subjects who experience a treatment-emergent cardiac arrhythmia that was felt to be, in the investigator's judgment, clinically significant, the investigator was to collect a standard 12-lead electro cardiology (ECG) at the time of the event, or within 2 hours following the event, and send a duplicate of the ECG to the designated central ECG reader.</p> |
| 08 July 2010     | <p>Regarding the primary and salvage EC inclusion criteria: In addition to symptoms consistent with EC, subjects who could not undergo esophagoscopy due to neutropenia, thrombocytopenia, or HIV/advanced AIDS, were to have culture-proven oropharyngeal candidiasis in order to qualify for study entry.</p>  |

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.

The study was prematurely terminated due to slow enrollment. The study was not terminated due to safety issues or concerns. Interpretation of the data are limited due to the small sample size and descriptive design.

Notes: