



## Clinical trial results:

### A PROSPECTIVE, OPEN-LABEL, NON-RANDOMIZED, MULTI-CENTER STUDY TO INVESTIGATE THE SAFETY AND TOLERABILITY OF VORICONAZOLE AS PRIMARY THERAPY FOR TREATMENT OF INVASIVE ASPERGILLOSIS AND MOLDS SUCH AS SCEDOSPORIUM OR FUSARIUM SPECIES IN PEDIATRIC PATIENTS

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2008-005275-10                   |
| Trial protocol           | NL HU CZ ES DE BG Outside EU/EEA |
| Global end of trial date | 15 May 2013                      |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 08 July 2016 |
| First version publication date | 25 July 2015 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | A1501080 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00836875 |
| 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)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000191-PIP01-08 |
| 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                       | 14 April 2014 |
| Is this the analysis of the primary completion data? | No            |

|                                  |             |
|----------------------------------|-------------|
| Global end of trial reached?     | Yes         |
| Global end of trial date         | 15 May 2013 |
| Was the trial ended prematurely? | Yes         |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of voriconazole as primary treatment of invasive aspergillosis (IA) and rare molds such as *Scedosporium* or *Fusarium* species in immunocompromised pediatric subjects from 2 to less than (<) 18 years of age.

Protection of trial subjects:

The study was in compliance with with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (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                          | 26 May 2009 |
| Long term follow-up planned                               | Yes         |
| Long term follow-up rationale                             | Safety      |
| Long term follow-up duration                              | 1 Months    |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Netherlands: 4    |
| Country: Number of subjects enrolled | Poland: 1         |
| Country: Number of subjects enrolled | Spain: 2          |
| Country: Number of subjects enrolled | Czech Republic: 1 |
| Country: Number of subjects enrolled | Thailand: 11      |
| Country: Number of subjects enrolled | Singapore: 5      |
| Country: Number of subjects enrolled | United States: 7  |
| Worldwide total number of subjects   | 31                |
| EEA total number of subjects         | 8                 |

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)                    | 11 |
| Adolescents (12-17 years)                | 20 |
| 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:

Study was started on 26 May 2009 and ended on 15 May 2013. Overall, 31 subjects were enrolled into the study across 7 countries.

### 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 possible, probable or proven IA.

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

Dosage and administration details:

For subjects aged 2 to <12 years, voriconazole was administered at a loading dose of 9 milligrams per kg (mg/kg), intravenously (IV) every 12 hours (q12h) for the first 24 hours, followed by maintenance IV dosing regimen of 8 mg/kg IV q12h for a minimum of 7 days. Once significant clinical improvement was observed, subjects could be switched to oral (PO) dosing regimen of 9 mg/kg (a maximum dose of 350 mg) PO q12h. Investigators used subject, tolerability and voriconazole trough plasma levels to facilitate dose adjustments. All subjects received voriconazole therapy for at least 6 weeks, up to a maximum of 12 weeks.

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

Arm description:

Subjects aged 12 to <18 years with possible, probable or proven IA.

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

Dosage and administration details:

For subjects aged 12 to <18 years (excluding those aged 12--14 years weighing <50 kg), voriconazole was administered at loading doses of 6 mg/kg, IV, q12h for the first 24 hours, followed by maintenance IV dosing regimen of 4 mg/kg IV q12h for a minimum of 7 days. Once significant clinical improvement was observed, subjects could be switched to oral dosing regimen of 200-300 mg PO q12h. Investigators used subject, tolerability and voriconazole trough plasma levels to facilitate dose adjustments. All subjects received voriconazole therapy for at least 6 weeks, up to a maximum of 12 weeks.

| <b>Number of subjects in period 1</b> | Voriconazole: 2 to<br><12 Years | Voriconazole: 12 to<br><18 Years |
|---------------------------------------|---------------------------------|----------------------------------|
| Started                               | 11                              | 20                               |
| Completed                             | 8                               | 17                               |
| Not completed                         | 3                               | 3                                |
| Consent withdrawn by subject          | -                               | 1                                |
| Death                                 | 3                               | 2                                |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Subjects aged 2 to <12 years with possible, probable or proven IA.

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

Reporting group description:

Subjects aged 12 to <18 years with possible, probable or proven IA.

| Reporting group values             | Voriconazole: 2 to <12 Years | Voriconazole: 12 to <18 Years | Total |
|------------------------------------|------------------------------|-------------------------------|-------|
| Number of subjects                 | 11                           | 20                            | 31    |
| Age categorical<br>Units: Subjects |                              |                               |       |

|   |              |               |    |
|---|--------------|---------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 7.9<br>± 2.3 | 14.1<br>± 1.7 | -  |
| Gender categorical<br>Units: Subjects                                   |              |               |    |
| Female  | 4            | 11            | 15 |
| Male  | 7            | 9             | 16 |

## 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 possible, probable or proven IA.  |                               |
| Reporting group title   | Voriconazole: 12 to <18 Years |
| Reporting group description:<br>Subjects aged 12 to <18 years with possible, probable or proven IA. |                               |

### Primary: Number of Subjects With Adverse Events (AEs)

|  |   |
|--|---|
| End point title  | Number of Subjects With Adverse Events (AEs) <sup>[1]</sup> |
| End point description:<br>Safety population: included all subjects who received at least 1 dose of study medication.                       |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline, daily while hospitalized, Days 7, 14, 28, 42, 84, 114, at end of treatment, up to 1 month post treatment |   |

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: Only descriptive data was planned to be reported for this end point.

| End point values                                   | Voriconazole: 2 to <12 Years | Voriconazole: 12 to <18 Years |  |  |
|--|------------------------------|-------------------------------|--|--|
| Subject group type                                 | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed                        | 11                           | 20                            |  |  |
| Units: Subjects                                    |                              |                               |  |  |
| With AEs   | 11                           | 19                            |  |  |
| With serious AEs                                   | 6                            | 9                             |  |  |
| With severe AEs                                    | 5                            | 8                             |  |  |
| Discontinued treatment due to AEs                  | 1                            | 0                             |  |  |
| Dose reduced or temporarily discontinued due to AE | 0                            | 4                             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With a Global Response of Success

|  |  |
|--|--|
| End point title  | Percentage of Subjects With a Global Response of Success |
| End point description:<br>Percentage of subjects with global response of success at Weeks 6 and at end of treatment (EOT) (up to Week 12). Global response of success was defined as a subject who achieved a complete or partial global response per the investigator. Complete response was defined as resolution of all clinical signs and symptoms PLUS resolution of 90 percent (%) or more of the lesions visible on radiological studies and attributed to invasive aspergillosis (IA) at Baseline. Partial response was defined as clinical improvement PLUS 50% to <90 % resolution of the radiological lesions attributed to IA at Baseline. |  |

Modified intent to treat (MITT) population: all subjects receiving at least 1 dose of study drug and diagnosed with proven or probable aspergillosis (defined by modified European Organization for Research and Treatment of Cancer Mycoses Study Group [EORTC/MSG] criteria) or microbiologically confirmed scedosporium or fusarium infection.

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| Weeks 6, EOT (up to Week 12) |           |

| End point values                 | Voriconazole: 2 to <12 Years | Voriconazole: 12 to <18 Years |  |  |
|----------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed      | 5                            | 9                             |  |  |
| Units: percentage of subjects    |                              |                               |  |  |
| number (confidence interval 95%) |                              |                               |  |  |
| Week 6                           | 40 (5.3 to 85.3)             | 77.8 (40 to 97.2)             |  |  |
| EOT                              | 40 (5.3 to 85.3)             | 77.8 (40 to 97.2)             |  |  |

## Statistical analyses

No statistical analyses for this end point

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

|  |   |
|--|---|
| End point title  | All-Cause Mortality - Number of Subjects Deaths |
| End point description:   |   |
| Number of subject deaths reported at Week 6 and at EOT (up to Week 12). Safety population. |   |
| End point type   | Secondary                                       |
| End point timeframe:   |   |
| Week 6, EOT (up to Week 12)  |   |

| End point values            | Voriconazole: 2 to <12 Years | Voriconazole: 12 to <18 Years |  |  |
|-----------------------------|------------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed | 11                           | 20                            |  |  |
| Units: Subjects             |                              |                               |  |  |
| Week 6                      | 3                            | 1                             |  |  |
| EOT                         | 0                            | 1                             |  |  |

## Statistical analyses



No statistical analyses for this end point

### Secondary: Attributable Mortality - Number of Subject Deaths

|  |   |
|--|---|
| End point title  | Attributable Mortality - Number of Subject Deaths |
| End point description:<br>Number of subject deaths attributable to study drug reported at Week 6 and at EOT (up to Week 12).<br>Safety population. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Weeks 6 and EOT (up to Week 12)  |   |

| End point values            | Voriconazole: 2 to <12 Years | Voriconazole: 12 to <18 Years |  |  |
|-----------------------------|------------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed | 11                           | 20                            |  |  |
| Units: Subjects             | 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>Safety population; only subjects who died were included in the analysis. |               |
| End point type   | Secondary     |
| End point timeframe:<br>Baseline up to 1 month post treatment                                      |               |

| End point values              | Voriconazole: 2 to <12 Years | Voriconazole: 12 to <18 Years |  |  |
|-------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type            | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed   | 3                            | 2                             |  |  |
| Units: days                   |                              |                               |  |  |
| median (full range (min-max)) | 30 (18 to 38)                | 47.5 (20 to 75)               |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline through the 1-month follow-up visit

Adverse event reporting additional description:

The same event may appear as both an AE and a Serious AE (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as non serious in another subject, or one subject may have experienced both a serious and non serious 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 possible, probable or proven IA.

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

Reporting group description:

Subjects aged 12 to <18 years with possible, probable or proven IA.

| Serious adverse events  | Voriconazole: 2 to <12 Years | Voriconazole: 12 to <18 Years |  |
|---|------------------------------|-------------------------------|--|
| Total subjects affected by serious adverse events                   |                              |                               |  |
| subjects affected / exposed   | 6 / 11 (54.55%)              | 9 / 20 (45.00%)               |  |
| number of deaths (all causes)                                       | 3                            | 2                             |  |
| number of deaths resulting from adverse events                      | 0                            | 0                             |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                              |                               |  |
| Acute lymphocytic leukaemia   |                              |                               |  |
| subjects affected / exposed   | 0 / 11 (0.00%)               | 2 / 20 (10.00%)               |  |
| occurrences causally related to treatment / all                     | 0 / 0                        | 0 / 3                         |  |
| deaths causally related to treatment / all                          | 0 / 0                        | 0 / 1                         |  |
| Vascular disorders  |                              |                               |  |
| Aneurysm ruptured   |                              |                               |  |
| subjects affected / exposed   | 1 / 11 (9.09%)               | 0 / 20 (0.00%)                |  |
| occurrences causally related to treatment / all                     | 0 / 1                        | 0 / 0                         |  |
| deaths causally related to treatment / all                          | 0 / 1                        | 0 / 0                         |  |
| Surgical and medical procedures                                     |                              |                               |  |
| Endotracheal intubation   |                              |                               |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary oedema                                |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Respiratory failure                             |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Cardiac arrest                                  |                |                |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure congestive                      |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Loss of consciousness                           |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Coagulopathy                                    |                |                |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Febrile neutropenia                             |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 2 / 20 (10.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Neutropenia                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Thrombocytopenia                                |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Eye disorders                                   |                |                 |  |
| Visual impairment                               |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Gingival bleeding                               |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lower gastrointestinal haemorrhage              |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Small intestinal haemorrhage                    |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                |                 |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Drug-induced liver injury                       |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Renal failure acute                             |                |                |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Muscular weakness                               |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Aspergillosis                                   |                |                |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis  |                |                |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 1 / 20 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Septic shock                                    |                |                |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 11 (18.18%) | 2 / 20 (10.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| <b>Metabolism and nutrition disorders</b>       |                 |                 |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 20 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 20 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| 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 |  |
|--|------------------------------|-------------------------------|--|
| <b>Total subjects affected by non-serious adverse events</b>               |                              |                               |  |
| subjects affected / exposed  | 10 / 11 (90.91%)             | 19 / 20 (95.00%)              |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                              |                               |  |
| Leukaemia  |                              |                               |  |
| subjects affected / exposed  | 0 / 11 (0.00%)               | 1 / 20 (5.00%)                |  |
| occurrences (all)  | 0                            | 1                             |  |
| <b>Vascular disorders</b>  |                              |                               |  |
| Flushing   |                              |                               |  |
| subjects affected / exposed  | 0 / 11 (0.00%)               | 1 / 20 (5.00%)                |  |
| occurrences (all)  | 0                            | 1                             |  |
| Haematoma  |                              |                               |  |
| subjects affected / exposed  | 0 / 11 (0.00%)               | 1 / 20 (5.00%)                |  |
| occurrences (all)  | 0                            | 1                             |  |
| Haemorrhage  |                              |                               |  |
| subjects affected / exposed  | 0 / 11 (0.00%)               | 1 / 20 (5.00%)                |  |
| occurrences (all)  | 0                            | 1                             |  |
| Hypertension   |                              |                               |  |
| subjects affected / exposed  | 0 / 11 (0.00%)               | 1 / 20 (5.00%)                |  |
| occurrences (all)  | 0                            | 2                             |  |

|   |                     |                       |  |
|---|---------------------|-----------------------|--|
| Hypotension<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1   |  |
| Phlebitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1   |  |
| General disorders and administration site conditions<br>Catheter site discharge<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1   |  |
| Catheter site pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 11 (9.09%)<br>3 | 2 / 20 (10.00%)<br>3  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>2   |  |
| Infusion site pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1   |  |
| Local swelling<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1   |  |
| Mucosal inflammation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0 | 3 / 20 (15.00%)<br>7  |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0 | 2 / 20 (10.00%)<br>3  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0 | 2 / 20 (10.00%)<br>5  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0 | 7 / 20 (35.00%)<br>10 |  |
| Reproductive system and breast disorders  |                     |                       |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Genital swelling                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 20 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Vulvar erosion                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 0 / 20 (0.00%)  |  |
| occurrences (all)                               | 1               | 0               |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Bronchospasm                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 2 / 11 (18.18%) | 2 / 20 (10.00%) |  |
| occurrences (all)                               | 2               | 2               |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 2 / 20 (10.00%) |  |
| occurrences (all)                               | 0               | 2               |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 11 (18.18%) | 4 / 20 (20.00%) |  |
| occurrences (all)                               | 2               | 9               |  |
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 0               | 1               |  |
| Nasal congestion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%)  | 2 / 20 (10.00%) |  |
| occurrences (all)                               | 1               | 3               |  |
| Oropharyngeal pain                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 2 / 20 (10.00%) |  |
| occurrences (all)                               | 0               | 2               |  |
| Pharyngeal inflammation                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 0               | 2               |  |
| Rales   |                 |                 |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                               | 2              | 0               |  |
| Tachypnoea                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)                               | 0              | 2               |  |
| Psychiatric disorders                           |                |                 |  |
| Affect lability                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 0              | 2               |  |
| Depression                                      |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                               | 1              | 0               |  |
| Insomnia  |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)                               | 0              | 2               |  |
| Investigations                                  |                |                 |  |
| Activated partial thromboplastin time prolonged |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                               | 1              | 0               |  |
| Alanine aminotransferase increased              |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)                               | 0              | 4               |  |
| Aspartate aminotransferase increased            |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 0              | 2               |  |
| Blood bilirubin increased                       |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 0              | 1               |  |
| Blood creatinine increased                      |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                               | 1              | 1               |  |
| Blood phosphorus decreased                      |                |                 |  |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                               | 1              | 0               |  |
| Blood potassium increased                       |                |                 |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed                    | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                              | 0              | 1               |  |
| Blood pressure increased                       |                |                 |  |
| subjects affected / exposed                    | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                              | 0              | 2               |  |
| Blood uric acid increased                      |                |                 |  |
| subjects affected / exposed                    | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                              | 0              | 1               |  |
| Cardiac murmur                                 |                |                 |  |
| subjects affected / exposed                    | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                              | 1              | 0               |  |
| Liver function test abnormal                   |                |                 |  |
| subjects affected / exposed                    | 0 / 11 (0.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)                              | 0              | 3               |  |
| Oxygen saturation decreased                    |                |                 |  |
| subjects affected / exposed                    | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                              | 0              | 1               |  |
| Prothrombin time prolonged                     |                |                 |  |
| subjects affected / exposed                    | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                              | 1              | 0               |  |
| Respirovirus test positive                     |                |                 |  |
| subjects affected / exposed                    | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                              | 0              | 2               |  |
| Transaminases increased                        |                |                 |  |
| subjects affected / exposed                    | 0 / 11 (0.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)                              | 0              | 4               |  |
| Weight decreased                               |                |                 |  |
| subjects affected / exposed                    | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                              | 0              | 2               |  |
| Injury, poisoning and procedural complications |                |                 |  |
| Allergic transfusion reaction                  |                |                 |  |
| subjects affected / exposed                    | 1 / 11 (9.09%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                              | 1              | 1               |  |
| Contusion                                      |                |                 |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 2 / 20 (10.00%)<br>3 |  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0  | 2 / 20 (10.00%)<br>3 |  |
| Incorrect drug administration rate<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 11 (9.09%)<br>2  | 0 / 20 (0.00%)<br>0  |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 11 (18.18%)<br>2 | 2 / 20 (10.00%)<br>2 |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 11 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1  |  |
| Nervous system disorders<br>Central nervous system lesion<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0  | 1 / 20 (5.00%)<br>4  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 11 (0.00%)<br>0  | 3 / 20 (15.00%)<br>4 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 1 / 11 (9.09%)<br>2  | 2 / 20 (10.00%)<br>3 |  |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 2 / 20 (10.00%)<br>3 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 1 / 20 (5.00%)<br>2  |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 1 / 20 (5.00%)<br>1  |  |
| Blood and lymphatic system disorders  |                      |                      |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Disseminated intravascular coagulation |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Febrile neutropenia                    |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)                      | 0              | 3               |  |
| Lymphadenitis                          |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Lymphopenia                            |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 0              | 2               |  |
| Neutropenia                            |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Neutrophilia                           |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 0              | 2               |  |
| Pancytopenia                           |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 2              | 0               |  |
| Thrombocytopenia                       |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 2 / 20 (10.00%) |  |
| occurrences (all)                      | 1              | 3               |  |
| Ear and labyrinth disorders            |                |                 |  |
| Ear haemorrhage                        |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Tinnitus                               |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Eye disorders                          |                |                 |  |
| Abnormal sensation in eye              |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Asthenopia                             |                |                 |  |

|                             |                |                 |
|-----------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 0              | 3               |
| Cataract                    |                |                 |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 0              | 2               |
| Chromatopsia                |                |                 |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 0              | 1               |
| Conjunctival haemorrhage    |                |                 |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Conjunctivitis              |                |                 |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all)           | 0              | 3               |
| Diplopia                    |                |                 |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 0              | 1               |
| Dry eye                     |                |                 |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 2              | 0               |
| Eye discharge               |                |                 |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |
| occurrences (all)           | 1              | 0               |
| Eye irritation              |                |                 |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 0              | 1               |
| Eye pain                    |                |                 |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 0              | 1               |
| Photophobia                 |                |                 |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 20 (5.00%)  |
| occurrences (all)           | 2              | 3               |
| Vision blurred              |                |                 |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 20 (15.00%) |
| occurrences (all)           | 0              | 4               |
| Visual impairment           |                |                 |

|                                  |                 |                 |  |
|----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 2               |  |
| Gastrointestinal disorders       |                 |                 |  |
| Abdominal distension             |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 2               |  |
| Abdominal pain                   |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 3 / 20 (15.00%) |  |
| occurrences (all)                | 0               | 5               |  |
| Abdominal pain upper             |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 1               |  |
| Anal fissure                     |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 1               |  |
| Constipation                     |                 |                 |  |
| subjects affected / exposed      | 1 / 11 (9.09%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 2               | 1               |  |
| Diarrhoea                        |                 |                 |  |
| subjects affected / exposed      | 3 / 11 (27.27%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 3               | 1               |  |
| Dysphagia                        |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 1               |  |
| Flatulence                       |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 2               |  |
| Gastritis                        |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 1               |  |
| Gastrooesophageal reflux disease |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 1               |  |
| Haematemesis                     |                 |                 |  |
| subjects affected / exposed      | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |  |
| occurrences (all)                | 0               | 1               |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Lip dry                                |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Mouth haemorrhage                      |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 1              | 2               |  |
| Mouth ulceration                       |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 2 / 20 (10.00%) |  |
| occurrences (all)                      | 1              | 2               |  |
| Nausea                                 |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 2 / 20 (10.00%) |  |
| occurrences (all)                      | 0              | 2               |  |
| Painful defaecation                    |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Proctalgia                             |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Rectal haemorrhage                     |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Upper gastrointestinal haemorrhage     |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Vomiting                               |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 1              | 2               |  |
| Hepatobiliary disorders                |                |                 |  |
| Jaundice cholestatic                   |                |                 |  |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 20 (5.00%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Skin and subcutaneous tissue disorders |                |                 |  |
| Decubitus ulcer                        |                |                 |  |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 20 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Dermatitis allergic                    |                |                 |  |

|                                       |                |                |
|---------------------------------------|----------------|----------------|
| subjects affected / exposed           | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all)                     | 1              | 0              |
| Dermatitis contact                    |                |                |
| subjects affected / exposed           | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all)                     | 1              | 0              |
| Dermatitis exfoliative                |                |                |
| subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                     | 0              | 2              |
| Dry skin                              |                |                |
| subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                     | 0              | 1              |
| Ecchymosis                            |                |                |
| subjects affected / exposed           | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all)                     | 1              | 0              |
| Erythema                              |                |                |
| subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                     | 0              | 2              |
| Heat rash                             |                |                |
| subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                     | 0              | 1              |
| Hyperhidrosis                         |                |                |
| subjects affected / exposed           | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all)                     | 1              | 0              |
| Ingrowing nail                        |                |                |
| subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                     | 0              | 1              |
| Petechiae                             |                |                |
| subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                     | 0              | 1              |
| Pigmentation disorder                 |                |                |
| subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all)                     | 0              | 2              |
| Post inflammatory pigmentation change |                |                |
| subjects affected / exposed           | 1 / 11 (9.09%) | 0 / 20 (0.00%) |
| occurrences (all)                     | 2              | 0              |



|                             |                 |                |  |
|-----------------------------|-----------------|----------------|--|
| Pruritus                    |                 |                |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 20 (5.00%) |  |
| occurrences (all)           | 0               | 1              |  |
| Rash                        |                 |                |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 20 (5.00%) |  |
| occurrences (all)           | 0               | 1              |  |
| Rash macular                |                 |                |  |
| subjects affected / exposed | 1 / 11 (9.09%)  | 1 / 20 (5.00%) |  |
| occurrences (all)           | 1               | 2              |  |
| Rash maculo-papular         |                 |                |  |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 20 (5.00%) |  |
| occurrences (all)           | 2               | 1              |  |
| Red man syndrome            |                 |                |  |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 20 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Scab                        |                 |                |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 20 (5.00%) |  |
| occurrences (all)           | 0               | 2              |  |
| Skin burning sensation      |                 |                |  |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 20 (0.00%) |  |
| occurrences (all)           | 1               | 0              |  |
| Skin lesion                 |                 |                |  |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 20 (0.00%) |  |
| occurrences (all)           | 3               | 0              |  |
| Toxic skin eruption         |                 |                |  |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 20 (0.00%) |  |
| occurrences (all)           | 2               | 0              |  |
| Urticaria                   |                 |                |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 20 (5.00%) |  |
| occurrences (all)           | 0               | 1              |  |
| Renal and urinary disorders |                 |                |  |
| Dysuria                     |                 |                |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 20 (5.00%) |  |
| occurrences (all)           | 0               | 1              |  |
| Pollakiuria                 |                 |                |  |

|   |                     |                      |  |
|---|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                      | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1  |  |
| Renal failure<br>subjects affected / exposed<br>occurrences (all)     | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1  |  |
| Urinary retention<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1  |  |
| Musculoskeletal and connective tissue disorders                       |                     |                      |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)        | 1 / 11 (9.09%)<br>1 | 0 / 20 (0.00%)<br>0  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)         | 0 / 11 (0.00%)<br>0 | 3 / 20 (15.00%)<br>6 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)     | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>4  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 11 (9.09%)<br>1 | 1 / 20 (5.00%)<br>1  |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)         | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>2  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | 2 / 20 (10.00%)<br>3 |  |
| Pain in jaw<br>subjects affected / exposed<br>occurrences (all)       | 1 / 11 (9.09%)<br>1 | 0 / 20 (0.00%)<br>0  |  |
| Infections and infestations   |                     |                      |  |
| Anal abscess<br>subjects affected / exposed<br>occurrences (all)      | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>2  |  |
| Bacteraemia   |                     |                      |  |

|   |                 |                 |
|---|-----------------|-----------------|
| subjects affected / exposed             | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |
| occurrences (all)                       | 0               | 2               |
| Bronchitis                              |                 |                 |
| subjects affected / exposed             | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |
| occurrences (all)                       | 0               | 2               |
| Cytomegalovirus infection               |                 |                 |
| subjects affected / exposed             | 1 / 11 (9.09%)  | 0 / 20 (0.00%)  |
| occurrences (all)                       | 1               | 0               |
| Device related infection                |                 |                 |
| subjects affected / exposed             | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |
| occurrences (all)                       | 0               | 1               |
| Implant site pustules                   |                 |                 |
| subjects affected / exposed             | 1 / 11 (9.09%)  | 0 / 20 (0.00%)  |
| occurrences (all)                       | 1               | 0               |
| Paronychia                              |                 |                 |
| subjects affected / exposed             | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |
| occurrences (all)                       | 0               | 1               |
| Postoperative wound infection           |                 |                 |
| subjects affected / exposed             | 1 / 11 (9.09%)  | 0 / 20 (0.00%)  |
| occurrences (all)                       | 1               | 0               |
| Sinusitis                               |                 |                 |
| subjects affected / exposed             | 0 / 11 (0.00%)  | 2 / 20 (10.00%) |
| occurrences (all)                       | 0               | 3               |
| Staphylococcal bacteraemia              |                 |                 |
| subjects affected / exposed             | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |
| occurrences (all)                       | 0               | 1               |
| Staphylococcal infection                |                 |                 |
| subjects affected / exposed             | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |
| occurrences (all)                       | 0               | 2               |
| Systemic candida                        |                 |                 |
| subjects affected / exposed             | 0 / 11 (0.00%)  | 1 / 20 (5.00%)  |
| occurrences (all)                       | 0               | 2               |
| Upper respiratory tract infection       |                 |                 |
| subjects affected / exposed             | 3 / 11 (27.27%) | 1 / 20 (5.00%)  |
| occurrences (all)                       | 4               | 1               |
| Viral upper respiratory tract infection |                 |                 |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0 | 1 / 20 (5.00%)<br>1 |  |
| Metabolism and nutrition disorders               |                     |                     |  |
| Fluid overload                                   |                     |                     |  |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 20 (5.00%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Fluid retention                                  |                     |                     |  |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 20 (5.00%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Hypercalcaemia                                   |                     |                     |  |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 20 (5.00%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Hyperkalaemia                                    |                     |                     |  |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 2 / 20 (10.00%)     |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Hyperuricaemia                                   |                     |                     |  |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 20 (5.00%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Hypoalbuminaemia                                 |                     |                     |  |
| subjects affected / exposed                      | 1 / 11 (9.09%)      | 1 / 20 (5.00%)      |  |
| occurrences (all)                                | 1                   | 1                   |  |
| Hypocalcaemia                                    |                     |                     |  |
| subjects affected / exposed                      | 3 / 11 (27.27%)     | 0 / 20 (0.00%)      |  |
| occurrences (all)                                | 3                   | 0                   |  |
| Hypokalaemia                                     |                     |                     |  |
| subjects affected / exposed                      | 1 / 11 (9.09%)      | 3 / 20 (15.00%)     |  |
| occurrences (all)                                | 2                   | 3                   |  |
| Hypomagnesaemia                                  |                     |                     |  |
| subjects affected / exposed                      | 2 / 11 (18.18%)     | 1 / 20 (5.00%)      |  |
| occurrences (all)                                | 2                   | 1                   |  |
| Hyponatraemia                                    |                     |                     |  |
| subjects affected / exposed                      | 2 / 11 (18.18%)     | 0 / 20 (0.00%)      |  |
| occurrences (all)                                | 3                   | 0                   |  |
| Hypophosphataemia                                |                     |                     |  |
| subjects affected / exposed                      | 3 / 11 (27.27%)     | 0 / 20 (0.00%)      |  |
| occurrences (all)                                | 6                   | 0                   |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 04 December 2008 | <ol style="list-style-type: none"><li>1. Added attributable mortality as a study endpoint.</li><li>2. Added Electrocardiography (ECGs) and vital signs to the primary analysis of AEs, tests and added significant ECG and vital signs changes to safety data summaries.</li><li>3. Added requirement for formal ophthalmologic exam(including fundoscopic exam) if a treatment-emergent visual AE was noted and added follow-up procedures for subjects with treatment-emergent visual AEs persisting at 1-month follow-up (FU) visit.</li><li>4. Expanded eligible diagnoses to include infection due to rare molds such as Scedosporium or Fusarium species and specified that mycology, histology, and cytology assessments were to be done at local site.</li><li>5. Clarified definition of discontinuation and required that discontinuations due to AEs be documented, reported immediately to the sponsor, and followed or referred for follow-up.</li><li>6. Added EOT as an analysis timepoint and the 6-week timepoint to global response assessment.</li><li>7. Changed primary analysis definition to include treatment-emergent AEs, ECGs, vital signs and not include physical examinations.</li><li>8. Added ECGs and vital signs to primary analysis of AEs, tests and added significant ECG and vital signs changes to safety data summaries.</li><li>9. Added text describing the option of an earlier switch to oral dosing.</li><li>10. Revised and clarified exclusion criteria.</li><li>11. Added a Week 6 treatment visit and defined the associated assessments and procedures.</li><li>12. Changed the time period for monitoring AEs to conclude with the 1-month FU visit.</li><li>13. Revised dosing recommendations for subjects with elevated voriconazole levels and clarified collection of plasma peak and trough samples.</li><li>14. Included male subjects in contraceptive guidelines and clarified the acceptability of complete abstinence.</li><li>15. Added Sections describing dose reductions and describing dose escalations.</li><li>16. Revised procedures for subjects discontinued for rescue therapy.</li><li>17. Reduced the samples for galactomannan assay at EOT from 2 to 1.</li></ol> |
| 14 July 2010     | <ol style="list-style-type: none"><li>1. Specified the approximate total blood sampling volume for a subject during the study and restricted the total volume to 150 milliliter (mL) or less.</li><li>2. Required that of the 15 subjects with proven or probable IA, a minimum of 10 subjects evaluable for safety were enrolled from the 2 to &lt;12 years age-group and stated that subjects would receive a total of 6 to 12 weeks of therapy.</li><li>3. Added the correlation between CYP2C19 genotype status and voriconazole exposure as an exploratory endpoint and added a requirement for the collection of 2 buccal swab samples at baseline or during the study.</li><li>4. Clarified the conditions for switching to oral voriconazole therapy and modified the dosing scheme and infusion rates.</li><li>5. Revised the requirements and recommendations for voriconazole level plasma sample collection on Day 3 and after dose adjustments.</li><li>6. Updated the dosing scheme for children (2 to &lt;12 years of age) and adolescents 12 to 14 years of age weighing less than 50 kg based on the results of 2 recently completed PK studies (A1501081 and A1501088) to allow enrollment in the younger age-group (children).</li><li>7. Added the requirement for assent from children who, per the investigator's judgment, were able to comprehend and as required by local regulations.</li></ol>  |

Notes:

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## **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 any safety issues or concerns. Interpretation of the data are limited due to the small sample size and descriptive design. |
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Notes: