# Clinical trial results:
# Open label study of isavuconazole in the treatment of patients with invasive Aspergillosis with renal impairment (RI) or of patients with invasive fungal disease (IFD) caused by rare moulds, yeasts or dimorphic fungi.

## Summary

| | |
|---|---|
| EudraCT number | 2006-005003-33 |
| Trial protocol | GB BE HU CZ DE ES |
| Global end of trial date | 05 May 2016 |

**Results information**

| | |
|---|---|
| Result version number | v3 (current) |
| This version publication date | 22 April 2017 |
| First version publication date | 05 June 2015 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 9766-CL-0103 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00634049 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Astellas Global Pharma Development, Inc |
| Sponsor organisation address | 1 Astellas Way, Northbrook, United States, |
| Public contact | Medical Head ID/IM/TX, Astellas Pharma Global Development, Astellas.resultsdisclosure@astellas.com |
| Scientific contact | Medical Head ID/IM/TX, Astellas Pharma Global Development, Astellas.resultsdisclosure@astellas.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? | No |

Notes:

**Results analysis stage**

| | |
|---|---|
| Analysis stage | Final |

| | |
|---|---|
| Date of interim/final analysis | 03 January 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 January 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 May 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Main objective of the trial was to describe the safety and efficacy of isavuconazole in the treatment of invasive Aspergillosis in patients with renal impairment (RI) or in patients with invasive fungal disease (IFD) caused by rare moulds, yeasts or dimorphic fungi.

Protection of trial subjects:

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

Background therapy:

Participants eligible for the study were primarily, but not limited to, those with underlying hematologic malignancies. Treatments for participants underlying disease were not standardized.

Evidence for comparator:

This study did not have a comparator arm. The choice of a uniform comparator for all patients included in this study was not feasible due to the allowance of patients with IFD caused by many different rare pathogens.

| | |
|---|---|
| Actual start date of recruitment | 21 April 2008 |
| 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 | Lebanon: 1 |
| Country: Number of subjects enrolled | Israel: 21 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | United States: 57 |
| Country: Number of subjects enrolled | Russian Federation: 2 |
| Country: Number of subjects enrolled | Mexico: 8 |
| Country: Number of subjects enrolled | Brazil: 20 |
| Country: Number of subjects enrolled | Thailand: 15 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 3 |
| Country: Number of subjects enrolled | India: 5 |
| Worldwide total number of subjects | 149 |
| EEA total number of subjects | 17 |

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) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 119 |
| From 65 to 84 years | 29 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Consenting participants with proven,probable or possible invasive Aspergillosis and RI or IFD caused by rare molds, yeasts or dimorphic fungi meeting the inclusion and none of the exclusion criteria were enrolled at multicenter study at 34 centers globally, including centers in the US, European Union, South America, Asia and the Middle East.

### Pre-assignment

Screening details:

Candidates for screening were male and female participants aged ≥18 years of age,at high risk for developing IFD caused by Aspergillus species,rare molds,yeasts,or other dimorphic fungi.Excluded participants had hepatic dysfunction,chronic aspergillosis, aspergilloma, allergic aspergillosis,advanced HIV or AIDS or were unlikely to survive 30 days.

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Isavuconazole |

Arm description:

Isavuconazole (BAL4815) is a broad spectrum triazole. It inhibits sterol 14 α-demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | isavuconazole/CRESEMBA |
| Investigational medicinal product code | BAL8557 |
| Other name | isavuconazonium sulfate,(CRESEMBA) as a pro drug of isavuconazole |
| Pharmaceutical forms | Capsule, Injection |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

The IV and oral formulations are 98% bioequivalent and therefore interchangable. A loading regimen of isavuconazole (IV or PO) was used over 2 days, followed by a maintenance regimen from Day 3 to EOT. During Days 1 and 2, three doses of 200 mg isavuconazole were administered every 8 hours for a total of six doses and from Day 3 to End of Treatment (EOT), maintanance dose of 200 mg isavuconazole was administered once daily up to 180 days; with an option for extended treatment under specified criteria.

| **Number of subjects in period 1** | Isavuconazole |
|---|---|
| Started | 149 |
| Completed | 146 |
| Not completed | 3 |
| Patient never received study drug | 1 |
| Patient died prior to receiving any study drug | 1 |
| Screening failure | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Isavuconazole |
| Reporting group description: | |
| Isavuconazole (BAL4815) is a broad spectrum triazole. It inhibits sterol 14 α-demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi. | |

| Reporting group values | Isavuconazole | Total | |
|---|---|---|---|
| Number of subjects | 149 | 149 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 116 | 116 | |
| From 65-84 years | 29 | 29 | |
| 85 years and over | 1 | 1 | |
| Not Recorded | 3 | 3 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 49.9 | | |
| standard deviation | ± 16.78 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 46 | 46 | |
| Male | 100 | 100 | |
| Not Recorded | 3 | 3 | |
| Race | | | |
| Race | | | |
| Units: Subjects | | | |
| White | 108 | 108 | |
| Black or African American | 10 | 10 | |
| Asian | 24 | 24 | |
| Other | 4 | 4 | |
| Not Recorded | 3 | 3 | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 22 | 22 | |
| Not Hispanic or Latino | 124 | 124 | |
| Not Recorded | 3 | 3 | |
| Therapy Status | | | |
| Intent to Treat Population. (ITT) | | | |
| Units: Subjects | | | |
| Primary Therapy | 93 | 93 | |

| | | | |
|---|---|---|---|
| Refractory | 38 | 38 | |
| Intolerant | 12 | 12 | |
| Missing | 3 | 3 | |
| Not Recorded | 3 | 3 | |
| Hematologic malignancy<br>Units: Subjects | | | |
| Yes | 63 | 63 | |
| No | 83 | 83 | |
| Not Recorded | 3 | 3 | |
| Allogeneic BMT/HSCT<br>Units: Subjects | | | |
| Yes | 26 | 26 | |
| No | 120 | 120 | |
| Not Recorded | 3 | 3 | |
| Uncontrolled malignancy status<br>Units: Subjects | | | |
| Yes | 46 | 46 | |
| No | 100 | 100 | |
| Not Recorded | 3 | 3 | |
| Corticosteroid use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes | 35 | 35 | |
| No | 111 | 111 | |
| Not Recorded | 3 | 3 | |
| T-cell immunosuppressant use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes | 61 | 61 | |
| No | 48 | 48 | |
| Missing | 37 | 37 | |
| Not Recorded | 3 | 3 | |
| Neutropenic<br>Units: Subjects | | | |
| Yes | 38 | 38 | |
| No | 66 | 66 | |
| Missing | 42 | 42 | |
| Not Recorded | 3 | 3 | |

## Subject analysis sets

| | |
|---|---|
| Subject analysis set title | mITT- Aspergillus [Renally Impaired] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Aspergillus - Renally Impaired mITT population consisted of participants who have had proven,probable or possible IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Renal impairment was defined as yes for patients who have a baseline eGFR-MDRD < 60 mL/min/1.73 m^2, no for patients who have a baseline eGFR-MDRD ≥ 60 mL/min/1.73 m^2. Overall there were 24 participants in the mITT-Aspergillus population out of which 20 participants were classified as Renally Impaired (RI).

| | |
|---|---|
| Subject analysis set title | mITT- Aspergillus [Not Renally Impaired] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Aspergillus - Renally Impaired mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Overall there were 24 participants in the mITT-Aspergillus population out of which 4 participants were classified as Not Renally Impaired (NRI).

| | |
|---|---|
| Subject analysis set title | mITT- Mucorales [Primary Therapy] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Mucorales – Primary Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 21 participants receiving isavuconazole as a primary therapy.

| | |
|---|---|
| Subject analysis set title | mITT- Mucorales [Refractory] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Mucorales – Refractory Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis).The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 11 participants whose IFD was refractory to prior AFT.

| | |
|---|---|
| Subject analysis set title | mITT - Mucorales [Intolerant] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Mucorales – Intolerant mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participant had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 5 participants who were intolerant to prior AFT.

| | |
|---|---|
| Subject analysis set title | mITT- Other Filamentous Fungi |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Filamentous Fungi mITT population consisted of 17 participants who have had proven or probable IFD as determined by the DRC caused by other filamentous fungi (4 Fusarium,2 Exophiala,2 Cladosporium,2 Scopulariopsis and 1 each of Acremonium, Alternaria, Curvularia,Exserohilum, Paecilomyces,Pseudallescheria and Scedosporium).

| | |
|---|---|
| Subject analysis set title | mITT- Mould Species |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Mould Species mITT population consisted of 7 participants who have had proven or probable IFD as determined by the DRC caused by mould species.

| | |
|---|---|
| Subject analysis set title | mITT- Dimorphic Fungi |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Dimorphic Fungi mITT population consisted of 29 participants who have had proven or probable IFD as determined by the DRC caused by dimorphic fungi (10 Paracoccidiodes,9 Coccidiodides, 7 Histoplasma, 3 Blastomyces).

| | |
|---|---|
| Subject analysis set title | mITT- Non Candida Yeast |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Non Candida Yeast mITT population consisted of 11 participants who have had proven or probable IFD as determined by the DRC caused by non-Candida yeast (4 Cryptococcus neoformans, 3 Cryptococcus gatii, 2 Cryptococcus NOS and 2 Trichosporon).

| | |
|---|---|
| Subject analysis set title | mITT-Mixed Infections |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Mixed Infections mITT population consisted of 15 participants who have had proven or probable IFD as determined by the DRC caused by mixed infections aspergillosis/mucormycosis.

| **Reporting group values** | mITT- Aspergillus [Renally Impaired] | mITT- Aspergillus [Not Renally Impaired] | mITT- Mucorales [Primary Therapy] |
|---|---|---|---|
| Number of subjects | 20 | 4 | 21 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 13 | 3 | 17 |
| From 65-84 years | 6 | 1 | 4 |
| 85 years and over | 1 | 0 | 0 |
| Not Recorded | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 55.7 | 41.5 | 51.7 |
| standard deviation | ± 20.65 | ± 25.72 | ± 14.72 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 8 | 1 | 4 |
| Male | 12 | 3 | 17 |
| Not Recorded | 0 | 0 | 0 |
| Race | | | |
| Race | | | |
| Units: Subjects | | | |
| White | 17 | 4 | 12 |
| Black or African American | 0 | 0 | 1 |
| Asian | 3 | 0 | 8 |
| Other | 0 | 0 | 0 |
| Not Recorded | 0 | 0 | 0 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 1 |
| Not Hispanic or Latino | 19 | 4 | 20 |
| Not Recorded | 0 | 0 | 0 |
| Therapy Status | | | |
| Intent to Treat Population. (ITT) | | | |
| Units: Subjects | | | |
| Primary Therapy | | | |
| Refractory | | | |
| Intolerant | | | |
| Missing | | | |
| Not Recorded | | | |
| Hematologic malignancy | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Yes | 11 | 3 | 11 |
| No | 9 | 1 | 10 |
| Not Recorded | 0 | 0 | 0 |
| Allogeneic BMT/HSCT<br>Units: Subjects | | | |
| Yes | 7 | 2 | 4 |
| No | 13 | 2 | 17 |
| Not Recorded | 0 | 0 | 0 |
| Uncontrolled malignancy status<br>Units: Subjects | | | |
| Yes | 5 | 2 | 11 |
| No | 15 | 2 | 10 |
| Not Recorded | 0 | 0 | 0 |
| Corticosteroid use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes | 12 | 1 | 5 |
| No | 8 | 3 | 16 |
| Not Recorded | 0 | 0 | 0 |
| T-cell immunosuppressant use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes | 15 | 3 | 7 |
| No | 5 | 1 | 14 |
| Missing | 0 | 0 | 0 |
| Not Recorded | 0 | 0 | 0 |
| Neutropenic<br>Units: Subjects | | | |
| Yes | 5 | 3 | 4 |
| No | 15 | 1 | 17 |
| Missing | 0 | 0 | 0 |
| Not Recorded | 0 | 0 | 0 |

| **Reporting group values** | mITT- Mucorales [Refractory] | mITT - Mucorales [Intolerant] | mITT- Other Filamentous Fungi |
|---|---|---|---|
| Number of subjects | 11 | 5 | 17 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 10 | 5 | 15 |
| From 65-84 years | 1 | 0 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Not Recorded | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 46.4 | 39.6 | 47.5 |
| standard deviation | ± 16.55 | ± 15.22 | ± 14.26 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 0 | 7 |
| Male | 8 | 5 | 10 |
| Not Recorded | 0 | 0 | 0 |
| Race | | | |
| Race | | | |
| Units: Subjects | | | |
| White | 10 | 3 | 13 |
| Black or African American | 1 | 2 | 1 |
| Asian | 0 | 0 | 3 |
| Other | 0 | 0 | 0 |
| Not Recorded | 0 | 0 | 0 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 1 |
| Not Hispanic or Latino | 11 | 5 | 16 |
| Not Recorded | 0 | 0 | 0 |
| Therapy Status | | | |
| Intent to Treat Population. (ITT) | | | |
| Units: Subjects | | | |
| Primary Therapy<br>Refractory<br>Intolerant<br>Missing<br>Not Recorded | | | |
| Hematologic malignancy<br>Units: Subjects | | | |
| Yes | 7 | 4 | |
| No | 4 | 1 | |
| Not Recorded | 0 | 0 | |
| Allogeneic BMT/HSCT<br>Units: Subjects | | | |
| Yes | 4 | 5 | |
| No | 7 | 0 | |
| Not Recorded | 0 | 0 | |
| Uncontrolled malignancy status<br>Units: Subjects | | | |
| Yes | 6 | 1 | |
| No | 5 | 4 | |
| Not Recorded | 0 | 0 | |
| Corticosteroid use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes | 3 | 2 | |
| No | 8 | 3 | |
| Not Recorded | 0 | 0 | |

| | | | |
|---|---|---|---|
| T-cell immunosuppressant use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes | 6 | 5 | |
| No | 5 | 0 | |
| Missing | 0 | 0 | |
| Not Recorded | 0 | 0 | |
| Neutropenic<br>Units: Subjects | | | |
| Yes | 5 | 1 | |
| No | 6 | 4 | |
| Missing | 0 | 0 | |
| Not Recorded | 0 | 0 | |

| **Reporting group values** | mITT- Mould Species | mITT- Dimorphic Fungi | mITT- Non Candida Yeast |
|---|---|---|---|
| Number of subjects | 7 | 29 | 11 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 4 | 24 | 7 |
| From 65-84 years | 3 | 5 | 4 |
| 85 years and over | 0 | 0 | 0 |
| Not Recorded | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 58.6 | 45.7 | 52.5 |
| standard deviation | ± 18.27 | ± 14.79 | ± 17.25 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 7 | 5 |
| Male | 5 | 22 | 6 |
| Not Recorded | 0 | 0 | 0 |
| Race | | | |
| Race | | | |
| Units: Subjects | | | |
| White | 5 | 20 | 6 |
| Black or African American | 1 | 2 | 1 |
| Asian | 1 | 4 | 3 |
| Other | 0 | 3 | 1 |
| Not Recorded | 0 | 0 | 0 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 17 | 2 |
| Not Hispanic or Latino | 7 | 12 | 9 |
| Not Recorded | 0 | 0 | 0 |

| Therapy Status | | | |
|---|---|---|---|
| Intent to Treat Population. (ITT) | | | |
| Units: Subjects | | | |
| Primary Therapy<br>Refractory<br>Intolerant<br>Missing<br>Not Recorded | | | |
| Hematologic malignancy<br>Units: Subjects | | | |
| Yes<br>No<br>Not Recorded | | | |
| Allogeneic BMT/HSCT<br>Units: Subjects | | | |
| Yes<br>No<br>Not Recorded | | | |
| Uncontrolled malignancy status<br>Units: Subjects | | | |
| Yes<br>No<br>Not Recorded | | | |
| Corticosteroid use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes<br>No<br>Not Recorded | | | |
| T-cell immunosuppressant use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes<br>No<br>Missing<br>Not Recorded | | | |
| Neutropenic<br>Units: Subjects | | | |
| Yes<br>No<br>Missing<br>Not Recorded | | | |

| **Reporting group values** | mITT-Mixed Infections | | |
|---|---|---|---|
| Number of subjects | 15 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |

| | | | |
|---|---|---|---|
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 13 | | |
| From 65-84 years | 2 | | |
| 85 years and over | 0 | | |
| Not Recorded | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 49.8 | | |
| standard deviation | ± 16.68 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | | |
| Male | 8 | | |
| Not Recorded | 0 | | |
| Race | | | |
| Race | | | |
| Units: Subjects | | | |
| White | 12 | | |
| Black or African American | 1 | | |
| Asian | 2 | | |
| Other | 0 | | |
| Not Recorded | 0 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | | |
| Not Hispanic or Latino | 15 | | |
| Not Recorded | 0 | | |
| Therapy Status | | | |
| Intent to Treat Population. (ITT) | | | |
| Units: Subjects | | | |
| Primary Therapy | | | |
| Refractory | | | |
| Intolerant | | | |
| Missing | | | |
| Not Recorded | | | |
| Hematologic malignancy | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Not Recorded | | | |
| Allogeneic BMT/HSCT | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |
| Not Recorded | | | |
| Uncontrolled malignancy status | | | |
| Units: Subjects | | | |
| Yes | | | |
| No | | | |

| | | | |
|---|---|---|---|
| Not Recorded | | | |
| Corticosteroid use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes<br>No<br>Not Recorded | | | |
| T-cell immunosuppressant use | | | |
| Intent-to-Treat Analysis Set | | | |
| Units: Subjects | | | |
| Yes<br>No<br>Missing<br>Not Recorded | | | |
| Neutropenic<br>Units: Subjects | | | |
| Yes<br>No<br>Missing<br>Not Recorded | | | |

### End points reporting groups

| | |
|---|---|
| Reporting group title | Isavuconazole |

Reporting group description:

Isavuconazole (BAL4815) is a broad spectrum triazole. It inhibits sterol 14 α-demethylase, a microsomal P450 enzyme (P45014DM) essential for ergosterol biosynthesis in fungi.

| | |
|---|---|
| Subject analysis set title | mITT- Aspergillus [Renally Impaired] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Aspergillus - Renally Impaired mITT population consisted of participants who have had proven,probable or possible IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Renal impairment was defined as yes for patients who have a baseline eGFR-MDRD < 60 mL/min/1.73 m^2, no for patients who have a baseline eGFR-MDRD ≥ 60 mL/min/1.73 m^2. Overall there were 24 participants in the mITT-Aspergillus population out of which 20 participants were classified as Renally Impaired (RI).

| | |
|---|---|
| Subject analysis set title | mITT- Aspergillus [Not Renally Impaired] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Aspergillus - Renally Impaired mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Classification by the DRC was based on the type of pathogen which was found to be the cause of participants IFD. The Aspergillus-mITT population was presented by renal status, renally impaired and not renally impaired. Overall there were 24 participants in the mITT-Aspergillus population out of which 4 participants were classified as Not Renally Impaired (NRI).

| | |
|---|---|
| Subject analysis set title | mITT- Mucorales [Primary Therapy] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Mucorales – Primary Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 21 participants receiving isavuconazole as a primary therapy.

| | |
|---|---|
| Subject analysis set title | mITT- Mucorales [Refractory] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Mucorales – Refractory Therapy mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participants had proven and 5 participants had probable invasive mucormycosis).The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 11 participants whose IFD was refractory to prior AFT.

| | |
|---|---|
| Subject analysis set title | mITT - Mucorales [Intolerant] |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Mucorales – Intolerant mITT population consisted of participants who have had proven or probable IFD as determined by the DRC. Based on the DRC assessment 37 participants were assessed to have proven or probable Mucorales infection (32 participant had proven and 5 participants had probable invasive mucormycosis). The DRC also categorized each patient by therapy status; these groups were primary therapy, refractory and intolerant. There were 5 participants who were intolerant to prior AFT.

| | |
|---|---|
| Subject analysis set title | mITT- Other Filamentous Fungi |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Filamentous Fungi mITT population consisted of 17 participants who have had proven or probable IFD as determined by the DRC caused by other filamentous fungi (4 Fusarium,2 Exophiala,2 Cladosporium,2 Scopulariopsis and 1 each of Acremonium, Alternaria, Curvularia,Exserohilum, Paecilomyces,Pseudallescheria and Scedosporium).

| | |
|---|---|
| Subject analysis set title | mITT- Mould Species |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Mould Species mITT population consisted of 7 participants who have had proven or probable IFD as determined by the DRC caused by mould species.

| | |
|---|---|
| Subject analysis set title | mITT- Dimorphic Fungi |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Dimorphic Fungi mITT population consisted of 29 participants who have had proven or probable IFD as determined by the DRC caused by dimorphic fungi (10 Paracoccidiodes,9 Coccidiodides, 7 Histoplasma, 3 Blastomyces).

| | |
|---|---|
| Subject analysis set title | mITT- Non Candida Yeast |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Non Candida Yeast mITT population consisted of 11 participants who have had proven or probable IFD as determined by the DRC caused by non-Candida yeast (4 Cryptococcus neoformans, 3 Cryptococcus gatii, 2 Cryptococcus NOS and 2 Trichosporon).

| | |
|---|---|
| Subject analysis set title | mITT-Mixed Infections |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Other Mixed Infections mITT population consisted of 15 participants who have had proven or probable IFD as determined by the DRC caused by mixed infections aspergillosis/mucormycosis.

## Primary: Crude success rate of overall outcome of treatment evaluated by the Data Review Committee (DRC) Day 42, Day 84 and EOT (mITT)

| | |
|---|---|
| End point title | Crude success rate of overall outcome of treatment evaluated by the Data Review Committee (DRC) Day 42, Day 84 and EOT (mITT)[1] |

End point description:

The DRC assessed overall response based on individual clinical, mycological and radiological response assessments. Participants with a complete or partial response were considered a success.

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

End point timeframe:

Day 42, Day 84 and End of Treatment [EOT]

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical inferences were made due to the non-comparative study design. However, study outcomes were tabulated by renal status and baseline organism to provide context to historic literature.

| End point values | mITT-Aspergillus [Renally Impaired] | mITT-Aspergillus [Not Renally Impaired] | mITT-Mucorales [Primary Therapy] | mITT-Mucorales [Refractory] |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 4 | 21 | 11 |
| Units: Percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 25 | 50 | 14.3 | 9.1 |
| Day 84 [Success] | 30 | 25 | 9.5 | 36.4 |
| End of Treatment [EOT Success] | 30 | 66.7 | 31.6 | 36.4 |

| End point values | mITT - Mucorales [Intolerant] | mITT- Other Filamentous Fungi | mITT- Mould Species | mITT- Dimorphic Fungi |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 17 | 7 | 29 |
| Units: Percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 0 | 47.1 | 28.6 | 41.4 |
| Day 84 [Success] | 20 | 41.2 | 28.6 | 44.8 |
| End of Treatment [EOT Success] | 20 | 64.7 | 28.6 | 64.3 |

| End point values | mITT- Non Candida Yeast | mITT-Mixed Infections | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 15 | | |
| Units: Percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 36.4 | 13.3 | | |
| Day 84 [Success] | 36.4 | 13.3 | | |
| End of Treatment [EOT Success] | 72.7 | 14.3 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: All-Cause Crude Mortality Through Day 42 and Day 84 (ITT)

| End point title | All-Cause Crude Mortality Through Day 42 and Day 84 (ITT) |
|---|---|

End point description:

All-cause Mortality was assessed through Day 42 and Day 84 and summarized for ITT population.

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

End point timeframe:

Baseline to End of Treatment (EOT [Day 180]).

| End point values | mITT- Aspergillus [Renally Impaired] | mITT- Aspergillus [Not Renally Impaired] | mITT- Mucorales [Primary Therapy] | mITT- Mucorales [Refractory] |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 4 | 21 | 4 |
| Units: Percent | | | | |
| number (not applicable) | | | | |
| All-cause Mortality Through Day 42 | 15 | 0 | 33.3 | 45.5 |
| All-cause Mortality Through Day 84 | 25 | 25 | 42.9 | 45.5 |

| End point values | mITT - Mucorales [Intolerant] | mITT- Other Filamentous Fungi | mITT- Mould Species | mITT- Dimorphic Fungi |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 17 | 7 | 29 |
| Units: Percent | | | | |
| number (not applicable) | | | | |
| All-cause Mortality Through Day 42 | 40 | 11.8 | 0 | 6.9 |
| All-cause Mortality Through Day 84 | 40 | 17.6 | 14.3 | 6.9 |

| End point values | mITT- Non Candida Yeast | mITT-Mixed Infections | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 15 | | |
| Units: Percent | | | | |
| number (not applicable) | | | | |
| All-cause Mortality Through Day 42 | 9.1 | 20 | | |
| All-cause Mortality Through Day 84 | 9.1 | 33.3 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Crude success rate of clinical response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)

| End point title | Crude success rate of clinical response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT) |
|---|---|

End point description:

The DRC evaluated clinical response to treatment for patients at day 42, day 84 and EOT. The list of possible clinical responses to treatment as assessed by the DRC is as follows; Success [Resolution of all attributable clinical symptoms and physical findings and Partial resolution of attributable clinical symptoms and physical findings], Failure [No resolution of any attributable clinical symptoms and physical findings and/or worsening and Not done or missing] and Not applicable [No attributable signs and symptoms present at baseline and no symptoms attributable to IFD developed post baseline]. Each type of clinical response to treatment evaluated by the DRC at day 42, day 84 and EOT were summarized.

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

End point timeframe:

Day 42, Day 84 and EOT

| End point values | mITT- Aspergillus [Renally Impaired] | mITT- Aspergillus [Not Renally Impaired] | mITT- Mucorales [Primary Therapy] | mITT- Mucorales [Refractory] |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 4 | 21 | 11 |
| Units: percent | | | | |

| number (not applicable) | | | | |
|---|---|---|---|---|
| Day 42 [Success] | 55 | 75 | 50 | 33.3 |
| Day 42 [Failure] | 45 | 25 | 50 | 66.7 |
| Day 84 [Success] | 45 | 25 | 40 | 22.2 |
| Day 84 [Failure] | 55 | 75 | 60 | 77.8 |
| EOT [Success] | 55 | 66.7 | 55.6 | 22.2 |
| EOT [Failure] | 45 | 33.3 | 44.4 | 77.8 |

| **End point values** | mITT - Mucorales [Intolerant] | mITT- Other Filamentous Fungi | mITT- Mould Species | mITT- Dimorphic Fungi |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 17 | 7 | 29 |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 50 | 78.6 | 71.4 | 85.2 |
| Day 42 [Failure] | 50 | 21.4 | 28.6 | 14.8 |
| Day 84 [Success] | 50 | 76.9 | 50 | 88.9 |
| Day 84 [Failure] | 50 | 23.1 | 50 | 11.1 |
| EOT [Success] | 50 | 81.3 | 85.7 | 82.1 |
| EOT [Failure] | 50 | 18.8 | 14.3 | 17.9 |

| **End point values** | mITT- Non Candida Yeast | mITT-Mixed Infections | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 15 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 77.8 | 50 | | |
| Day 42 [Failure] | 22.2 | 50 | | |
| Day 84 [Success] | 77.8 | 50 | | |
| Day 84 [Failure] | 22.2 | 50 | | |
| EOT [Success] | 70 | 38.5 | | |
| EOT [Failure] | 30 | 61.5 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Crude success rate of mycological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)

| End point title | Crude success rate of mycological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT) |
|---|---|

End point description:

The DRC evaluated mycological response to treatment for patients at day 42, day 84 and EOT. The list

of possible mycological responses to treatment is as follows, Success [Eradication and Presumed eradication], Failure [Persistence, Presumed persistence and Not done or missing] and Not applicable [No mycological evidence available at baseline]. Each type of mycological response to treatment evaluated by the DRC at day 42, day 84 and EOT was summarized.

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

End point timeframe:

Day 42, Day 84 and End of Treatment (EOT).

| **End point values** | mITT-Aspergillus [Renally Impaired] | mITT-Aspergillus [Not Renally Impaired] | mITT-Mucorales [Primary Therapy] | mITT-Mucorales [Refractory] |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 4 | 21 | 11 |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 30 | 50 | 4.8 | 0 |
| Day 42 [Failure] | 70 | 50 | 95.2 | 100 |
| Day 84 [Success] | 35 | 25 | 9.5 | 27.3 |
| Day 84 [Failure] | 65 | 75 | 90.5 | 72.7 |
| EOT [Success] | 35 | 66.7 | 31.6 | 36.4 |
| EOT [Failure] | 65 | 33.3 | 68.4 | 63.6 |

| **End point values** | mITT - Mucorales [Intolerant] | mITT- Other Filamentous Fungi | mITT- Mould Species | mITT-Dimorphic Fungi |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 17 | 7 | 29 |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 0 | 29.4 | 28.6 | 27.6 |
| Day 42 [Failure] | 100 | 70.6 | 71.4 | 72.4 |
| Day 84 [Success] | 40 | 35.3 | 28.6 | 27.6 |
| Day 84 [Failure] | 60 | 64.7 | 71.4 | 72.4 |
| EOT [Success] | 40 | 70.6 | 28.6 | 53.6 |
| EOT [Failure] | 60 | 29.4 | 71.4 | 46.4 |

| **End point values** | mITT- Non Candida Yeast | mITT-Mixed Infections | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 15 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 45.5 | 13.3 | | |
| Day 42 [Failure] | 54.5 | 86.7 | | |
| Day 84 [Success] | 45.5 | 13.3 | | |

| | | | | |
|---|---|---|---|---|
| Day 84 [Failure] | 54.5 | 86.7 | | |
| EOT [Success] | 81.8 | 14.3 | | |
| EOT [Failure] | 18.2 | 85.7 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Crude success rate of radiological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT)

| | |
|---|---|
| End point title | Crude success rate of radiological response to treatment evaluated by the Data Review Committee (DRC) at Day 42, 84 and EOT (mITT) |

End point description:

Radiological responses to treatment as assessed by the DRC at different time points are as follows, Day 42-Success [Improvement of at least 25% from baseline for invasive aspergillosis and other filamentous mold infections],Failure [No postbaseline radiology available]; Day 84-Success [Improvement of at least 50% from baseline for invasive aspergillosis and other filamentous mold infections], Failure [No postbaseline radiology available for patient with baseline evidence of radiologic disease]; EOT-Success [Improvement of at least 25% from baseline if EOT occurs prior to day 42 and at least 50% improvement from baseline if EOT occurs after day 42 for invasive aspergillosis and other filamentous mold infections], Failure [No postbasline radiology available].

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

End point timeframe:

Day 42, Day 84 and EOT

| **End point values** | mITT-Aspergillus [Renally Impaired] | mITT-Aspergillus [Not Renally Impaired] | mITT-Mucorales [Primary Therapy] | mITT-Mucorales [Refractory] |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 4 | 21 | 11 |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 30 | 25 | 0 | 10 |
| Day 42 [Failure] | 70 | 75 | 100 | 90 |
| Day 84 [Success] | 20 | 25 | 4.8 | 20 |
| Day 84 [Failure] | 80 | 75 | 95.2 | 80 |
| EOT [Success] | 15 | 66.7 | 16.7 | 20 |
| EOT [Failure] | 85 | 33.3 | 83.3 | 80 |

| **End point values** | mITT - Mucorales [Intolerant] | mITT- Other Filamentous Fungi | mITT- Mould Species | mITT-Dimorphic Fungi |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 5 | 17 | 7 | 29 |
| Units: percent | | | | |
| number (not applicable) | | | | |

| | | | | |
|---|---|---|---|---|
| Day 42 [Success] | 0 | 25 | 16.7 | 21.4 |
| Day 42 [Failure] | 100 | 75 | 83.3 | 78.6 |
| Day 84 [Success] | 20 | 6.3 | 0 | 28.6 |
| Day 84 [Failure] | 80 | 93.8 | 100 | 71.4 |
| EOT [Success] | 20 | 50 | 0 | 33.3 |
| EOT [Failure] | 80 | 50 | 100 | 66.7 |

| **End point values** | mITT- Non Candida Yeast | mITT-Mixed Infections | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 11 | 15 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Day 42 [Success] | 0 | 7.1 | | |
| Day 42 [Failure] | 100 | 92.9 | | |
| Day 84 [Success] | 10 | 14.3 | | |
| Day 84 [Failure] | 90 | 85.7 | | |
| EOT [Success] | 10 | 7.7 | | |
| EOT [Failure] | 90 | 92.3 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Patients were assessed for the occurrence of AEs on an ongoing basis during the course of the study and up to follow-up visit 1 (28 days after the last administration of study drug).

Adverse event reporting additional description:

All adverse events analysis was completed on Safety Analysis Set (SAF) population. Adverse events reported are Treatment Emergent Adverse Events (TEAEs). A treatment- emergent adverse event is any adverse event that starts after the first administration of study medication until 28 days after the last dose of study medication.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 12.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Not Renally Impaired |
| Reporting group description: - | |
| Reporting group title | Renally Impaired |

Reporting group description: -

| Serious adverse events | Not Renally Impaired | Renally Impaired | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 46 / 87 (52.87%) | 43 / 59 (72.88%) | |
| number of deaths (all causes) | 23 | 24 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Arteritis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and | | | |

| | | | |
|---|---|---|---|
| unspecified (incl cyst and polyps) | | | |
| Acute lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute myeloid leukaemia recurrent | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chronic lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Leukaemia recurrent | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Immune system disorders | | | |
| Acute graft versus host disease | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft versus host disease | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Lung transplant rejection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Aggression | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Agitation | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hallucination | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Electromechanical dissociation | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| 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 | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 3 / 87 (3.45%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypercapnia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Hypoxia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary alveolar haemorrhage | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 4 / 59 (6.78%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sinus disorder | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wheezing | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (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 | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic transformation stroke | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to | 0 / 0 | 1 / 1 | |

| | | | |
|---|---|---|---|
| treatment / all | | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 87 (3.45%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 3 / 59 (5.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised intraabdominal fluid collection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis chronic | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis relapsing | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 87 (4.60%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Renal and urinary disorders** | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 4 / 59 (6.78%) | |
| occurrences causally related to | 0 / 1 | 1 / 4 | |

| | | | |
|---|---|---|---|
| treatment / all | | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangiolitis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic lupus erythematosus | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (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 | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspergillosis | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| BK virus infection | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 3 / 59 (5.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchiectasis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus enteritis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal sepsis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung infection pseudomonal | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mucormycosis | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 87 (6.90%) | 1 / 59 (1.69%) | |

| | | | |
|---|---|---|---|
| occurrences causally related to treatment / all | 0 / 8 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia blastomyces | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia primary atypical | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pseudomonas bronchitis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| 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 / 87 (1.15%) | 2 / 59 (3.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |

| | | |
|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 |
| Septic shock | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 6 / 59 (10.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 4 |
| Sinusitis | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Sinusitis fungal | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |
| Staphylococcal bacteraemia | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 |
| Streptococcal bacteraemia | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Brain abscess | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral diarrhoea | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 59 (1.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Zygomycosis | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 0 / 59 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Not Renally Impaired | Renally Impaired | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 68 / 87 (78.16%) | 54 / 59 (91.53%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 3 / 59 (5.08%) | |
| occurrences (all) | 5 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 5 / 59 (8.47%) | |
| occurrences (all) | 5 | 5 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 7 / 87 (8.05%) | 1 / 59 (1.69%) | |
| occurrences (all) | 8 | 1 | |
| Chills | | | |
| subjects affected / exposed | 3 / 87 (3.45%) | 5 / 59 (8.47%) | |
| occurrences (all) | 3 | 8 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 4 / 59 (6.78%) | |
| occurrences (all) | 2 | 5 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 87 (9.20%) | 8 / 59 (13.56%) | |
| occurrences (all) | 8 | 11 | |
| Pain | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 3 / 59 (5.08%) | |
| occurrences (all) | 3 | 4 | |
| Pyrexia | | | |
| subjects affected / exposed | 15 / 87 (17.24%) | 9 / 59 (15.25%) | |
| occurrences (all) | 27 | 14 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 7 / 59 (11.86%) | |
| occurrences (all) | 2 | 9 | |
| Insomnia | | | |
| subjects affected / exposed | 8 / 87 (9.20%) | 5 / 59 (8.47%) | |
| occurrences (all) | 9 | 8 | |
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 6 / 87 (6.90%) | 4 / 59 (6.78%) | |
| occurrences (all) | 6 | 4 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 3 / 59 (5.08%) | |
| occurrences (all) | 2 | 4 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 4 / 59 (6.78%) | |
| occurrences (all) | 2 | 4 | |

| | | | |
|---|---|---|---|
| Sinus tachycardia | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 3 / 59 (5.08%) | |
| occurrences (all) | 2 | 3 | |
| Tachycardia | | | |
| subjects affected / exposed | 4 / 87 (4.60%) | 4 / 59 (6.78%) | |
| occurrences (all) | 5 | 4 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 4 / 59 (6.78%) | |
| occurrences (all) | 2 | 4 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 6 / 59 (10.17%) | |
| occurrences (all) | 2 | 6 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 12 / 87 (13.79%) | 3 / 59 (5.08%) | |
| occurrences (all) | 14 | 3 | |
| Epistaxis | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 2 / 59 (3.39%) | |
| occurrences (all) | 6 | 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 87 (8.05%) | 6 / 59 (10.17%) | |
| occurrences (all) | 7 | 6 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 3 / 59 (5.08%) | |
| occurrences (all) | 1 | 3 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 4 / 59 (6.78%) | |
| occurrences (all) | 3 | 4 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 3 / 59 (5.08%) | |
| occurrences (all) | 5 | 3 | |
| Headache | | | |
| subjects affected / exposed | 14 / 87 (16.09%) | 11 / 59 (18.64%) | |
| occurrences (all) | 19 | 13 | |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 87 (4.60%) | 7 / 59 (11.86%) | |
| occurrences (all) | 4 | 8 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 1 / 59 (1.69%) | |
| occurrences (all) | 5 | 2 | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 87 (11.49%) | 16 / 59 (27.12%) | |
| occurrences (all) | 11 | 22 | |
| Constipation | | | |
| subjects affected / exposed | 10 / 87 (11.49%) | 5 / 59 (8.47%) | |
| occurrences (all) | 11 | 5 | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 3 / 59 (5.08%) | |
| occurrences (all) | 1 | 3 | |
| Nausea | | | |
| subjects affected / exposed | 14 / 87 (16.09%) | 19 / 59 (32.20%) | |
| occurrences (all) | 19 | 23 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 3 / 59 (5.08%) | |
| occurrences (all) | 0 | 3 | |
| Vomiting | | | |
| subjects affected / exposed | 17 / 87 (19.54%) | 16 / 59 (27.12%) | |
| occurrences (all) | 26 | 24 | |
| Renal and urinary disorders | | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 3 / 59 (5.08%) | |
| occurrences (all) | 1 | 3 | |
| Oliguria | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 3 / 59 (5.08%) | |
| occurrences (all) | 0 | 3 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 7 / 87 (8.05%) | 2 / 59 (3.39%) | |
| occurrences (all) | 7 | 2 | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|---|---|---|
| disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 3 / 59 (5.08%) | |
| occurrences (all) | 5 | 4 | |
| Back pain | | | |
| subjects affected / exposed | 8 / 87 (9.20%) | 6 / 59 (10.17%) | |
| occurrences (all) | 8 | 6 | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 3 / 59 (5.08%) | |
| occurrences (all) | 2 | 4 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 87 (3.45%) | 4 / 59 (6.78%) | |
| occurrences (all) | 4 | 4 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 6 / 87 (6.90%) | 4 / 59 (6.78%) | |
| occurrences (all) | 7 | 4 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 87 (4.60%) | 3 / 59 (5.08%) | |
| occurrences (all) | 6 | 3 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 4 / 87 (4.60%) | 7 / 59 (11.86%) | |
| occurrences (all) | 5 | 8 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 3 / 59 (5.08%) | |
| occurrences (all) | 1 | 3 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 6 / 87 (6.90%) | 6 / 59 (10.17%) | |
| occurrences (all) | 8 | 6 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 87 (3.45%) | 3 / 59 (5.08%) | |
| occurrences (all) | 3 | 3 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 3 / 59 (5.08%) | |
| occurrences (all) | 0 | 3 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 7 / 87 (8.05%) | 2 / 59 (3.39%) | |

| | | | |
|---|---|---|---|
| occurrences (all) | 7 | 2 | |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Clostridial infection | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 3 / 59 (5.08%) | |
| occurrences (all) | 0 | 3 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 3 / 59 (5.08%) | |
| occurrences (all) | 1 | 4 | |
| Herpes zoster | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 1 / 59 (1.69%) | |
| occurrences (all) | 7 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 87 (6.90%) | 5 / 59 (8.47%) | |
| occurrences (all) | 7 | 6 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 87 (2.30%) | 7 / 59 (11.86%) | |
| occurrences (all) | 2 | 7 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 October 2007 | Amendment 1 issued on October 16, 2007, clarified the type of participants to be enrolled, including changes requested by Regulatory Authorities. Clarifications were made to the duration of study drug, clinical and mycological responses, and to the timing of evaluations for secondary efficacy variables including the addition that survival status should be assessed for all participants, including those discontinued prior to day 42 or day 84 due to an unsuccessful outcome. The ceiling for total bilirubin, aspartate transaminase (AST) and alanine transaminase (ALT) abnormalities were decreased per regulatory advice. The estimated number of centers that participated in the study was adjusted from 200 to 150. |
| 27 May 2010 | Amendment 2 issued on May 27, 2010, identified the change in the study sponsorship from Basilea to Astellas. The project physician, biostatistician and clinical pharmacologist were also changed. Isavuconazole dosing and the fasting requirement for oral isavuconazole administration were amended. The prohibited concomitant drugs were updated. The European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions of IFD were changed from 2002 to the revised 2008 criteria. |
| 17 November 2010 | Amendment 3 issued on November 17, 2010, amended maximum duration of therapy from 84 days up to 180 days and the timing of the first study drug maintenance dose was also amended. The primary and secondary analysis and efficacy variables were amended to specify that outcome criteria were assessed by the DRC and Investigator and to add additional time points for analysis. The exploratory analysis variables were amended to specify pharmacokinetic analysis and the addition of analysis of serum galactomannan (GM) as a biomarker for treatment of invasive aspergillosis. The inclusion and exclusion criteria were also amended and clarified. The criterion for withdrawing participants with possible IFD was removed, and prohibited and cautionary drugs and drug-drug interactions (DDIs) were updated. Various study procedures in the Schedule of Assessments were amended, clarified and added. Bronchoalveolar lavage (BAL) galactomannan (GM) was clarified as mycological criteria for enrollment of participants with invasive aspergillosis. The Protocol was amended to classify these participants as possible versus probable cases of IFD. Additional follow-up criteria for enrollment of these participants were also added. The CLCr calculation was amended to standardize reporting; ideal rather than actual BW was used in the calculation. The laboratory tests albumin, p-amylase and lipase were also added, and an improvement of < 25% was included in radiological response criteria. |
| 11 June 2012 | Amendment 5 issued on June 11, 2012, amended and clarified the efficacy variables and analysis sets and modified the entry criteria. Entry criteria changes included allowance of enrollment of participants on dialysis and of participants with proven or probable invasive mucormycosis who required primary therapy, and exclusion of participants who were enrolled in previous isavuconazole trials. Sirolimus and tyrosine kinase inhibitors were added as medications to use with caution, and clarification was added that statins could be discontinued at time of first dose. Various study procedures were amended, clarified and added to the Schedule of Assessments. The laboratory tests hematocrit and blood, urea and nitrogen test (BUN) were added. |

| | |
|---|---|
| 06 February 2013 | Amendment 6.1 issued on February 06, 2013, added inclusion criterion 7, stating that participants were not to participate in any other clinical trial within 30 days prior to first administration of study drug. Exclusion criterion 12 was revised to remove the exception that allowed concurrent participation in open-label protocols; limited the enrollment to participants that had proven or probable IFD caused by rare molds, yeasts or dimorphic fungi and participants who had proven or probable invasive zycomycosis who required primary treatment; relabeled inclusion criterion 5 as inclusion criterion 6; and clarified that no waivers to inclusion or exclusion criteria were permitted. The total sample size was increased from 100 participants to 150 participants to allow enrollment of specified subsets of participants requiring primary therapy. As the sample size was increased and the inclusion of participants with specific infections was limited, the sections of the Protocol that were no longer relevant to participants to be enrolled under this amendment were identified, and exclusion criterion 15 was removed to allow the inclusion of participants with invasive aspergillosis. A section entitled End of Trial in All Participating Countries was added to the Protocol, to define the end of trial for this Protocol and allow for consistency throughout participating countries. The Protocol was also updated to indicate that preliminary data suggested isavuconazole may shorten the QT interval. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 01 January 2009 | Enrollment in the clinical study was suspended in January 2009 pending further characterization of newly identified impurities. After successful completion of the studies, regulatory notifications, and transfer of Sponsorship from Basilea to Astellas, resumption of enrollment occurred in April 2011 for the 9766-CL-0103/WSA-CS-003 study (hereafter referred to as 9766-CL-0103). | 01 April 2011 |

Notes:

## Limitations and caveats

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

| |
|---|
| Primary limitation is the non-comparative design. Conduct of a large randomized controlled study in these rare diseases was not considered feasible. The results provide evidence that CRESEMBA is effective for the treatment for mucormycosis. |

Notes: