# Clinical trial results:
# A Phase III, Double-Blind, Randomized Study to Evaluate the Safety and Efficacy of BAL8557 Versus a Caspofungin Followed by Voriconazole Regimen in the Treatment of Candidemia and Other Invasive Candida Infections

## Summary

| | |
|---|---|
| EudraCT number | 2006-003951-18 |
| Trial protocol | BE DE HU ES NL IT GB |
| Global end of trial date | 03 March 2015 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 July 2016 |
| First version publication date | 29 July 2016 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 9766-CL-0105 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00413218 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Astellas Study Drug Name: Isavuconazonium sulfate (BAL8557/ASP9766) |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Astellas Pharma Global Development, Inc. |
| Sponsor organisation address | One Astellas Way, Northbrook, United States, 60062 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 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 March 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 March 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to compare the efficacy of treatment with isavuconazole versus caspofungin in participants with candidemia or other invasive Candida infections and examine safety and tolerability of treatment with isavuconazole versus caspofungin/voriconazole regimen.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 08 March 2007 |
| 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 | Argentina: 15 |
| Country: Number of subjects enrolled | Australia: 6 |
| Country: Number of subjects enrolled | Belgium: 39 |
| Country: Number of subjects enrolled | Brazil: 25 |
| Country: Number of subjects enrolled | Canada: 18 |
| Country: Number of subjects enrolled | Chile: 4 |
| Country: Number of subjects enrolled | China: 2 |
| Country: Number of subjects enrolled | France: 14 |
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | India: 26 |
| Country: Number of subjects enrolled | Israel: 72 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Lebanon: 4 |
| Country: Number of subjects enrolled | Malaysia: 5 |
| Country: Number of subjects enrolled | Mexico: 10 |
| Country: Number of subjects enrolled | New Zealand: 2 |

| | |
|---|---|
| Country: Number of subjects enrolled | Philippines: 3 |
| Country: Number of subjects enrolled | South Africa: 3 |
| Country: Number of subjects enrolled | Russian Federation: 4 |
| Country: Number of subjects enrolled | Singapore: 8 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | Thailand: 82 |
| Country: Number of subjects enrolled | United States: 56 |
| Worldwide total number of subjects | 450 |
| EEA total number of subjects | 102 |

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) | 276 |
| From 65 to 84 years | 157 |
| 85 years and over | 17 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were stratified by geographical region (North America; Western Europe plus Australia and New Zealand; or Other Regions) and baseline neutropenic status (presence vs absence) defined as absolute neutrophil count (ANC) < 0.5 x 10^9/L [< 500/mm^3] for ≥ 10 days.

### Pre-assignment

Screening details:

Consenting male and female participants aged ≥ 18 with candidemia or an invasive Candida infection who had a positive blood or tissue culture obtained within 96 hours prior to randomization and meeting the inclusion/exclusion criteria were enrolled in the study.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 450 |
| Number of subjects completed | 440 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Participants didn't meet incl/excl: 4 |
| Reason: Number of subjects | Participants didn't take study drug: 6 |

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Blinding implementation details:

Participants were randomized 1:1 to receive either isavuconazole or caspofungin in a blinded way. The sponsor, contract research organization (CRO) staff, investigators, participants and study coordinator(s) were blinded to randomization of study drug.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Isavuconazole (ISA) |

Arm description:

Participants received 3 intravenous (IV) loading doses of 200 mg of isavuconazole on days 1 and 2, followed by an IV maintenance dose of 200 mg once daily from day 3 to day 56. On day 11 at the discretion of the investigator, non-neutropenic participants could switch from IV to oral therapy. Oral therapy consisted of 200 mg isavuconazole once daily.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Isavuconazole |
| Investigational medicinal product code | BAL8557 |
| Other name | |
| Pharmaceutical forms | Powder for infusion, Capsule |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Isavuconazole for IV administration was provided as lyophilized powder for IV infusion. Isavuconazole (200 mg) was dissolved in 250 mL of a compatible infusion solution.

| | |
|---|---|
| **Arm title** | Caspofungin (CAS)/Voriconazole |

Arm description:

Participants received 1 intravenous (IV) loading dose of 70 mg CAS on day 1, followed by an IV

maintenance dose of 50 mg CAS from day 2 to day 56. On day 11 at the discretion of the investigator, non-neutropenic participants could switch from IV CAS to oral voriconazole comprising of a loading dose of 400 mg twice daily (BID) on the first day of oral therapy followed by standard dosing of 200 mg BID thereafter.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Voriconazole |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

For oral therapy, over-encapsulated voriconazole tablets were provided. Each tablet contained 200 mg of voriconazole.

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

Dosage and administration details:

Caspofungin for IV administration was provided as a lyophilized powder. Caspofungin (50 or 70 mg) was dissolved in 250 mL of a compatible infusion solution.

| **Number of subjects in period 1[1]** | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole |
|---|---|---|
| Started | 221 | 219 |
| Completed | 120 | 131 |
| Not completed | 101 | 88 |
| Adverse event, serious fatal | 57 | 56 |
| Consent withdrawn by subject | 9 | 1 |
| Admin/Other | 20 | 14 |
| Lost to follow-up | 14 | 17 |
| Missing | 1 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Four hundred and fifty participants were randomized in the study however 10 participants did not receive treatment.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Isavuconazole (ISA) |
| Reporting group description: | |
| Participants received 3 intravenous (IV) loading doses of 200 mg of isavuconazole on days 1 and 2, followed by an IV maintenance dose of 200 mg once daily from day 3 to day 56. On day 11 at the discretion of the investigator, non-neutropenic participants could switch from IV to oral therapy. Oral therapy consisted of 200 mg isavuconazole once daily. | |
| Reporting group title | Caspofungin (CAS)/Voriconazole |
| Reporting group description: | |
| Participants received 1 intravenous (IV) loading dose of 70 mg CAS on day 1, followed by an IV maintenance dose of 50 mg CAS from day 2 to day 56. On day 11 at the discretion of the investigator, non-neutropenic participants could switch from IV CAS to oral voriconazole comprising of a loading dose of 400 mg twice daily (BID) on the first day of oral therapy followed by standard dosing of 200 mg BID thereafter. | |

| Reporting group values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | Total |
|---|---|---|---|
| Number of subjects | 221 | 219 | 440 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 58 | 57.9 | |
| standard deviation | ± 17.54 | ± 16.88 | - |
| Gender categorical<br>Units: | | | |
| Male | 143 | 126 | 269 |
| Female | 78 | 93 | 171 |

## End points

### End points reporting groups

| Reporting group title | Isavuconazole (ISA) |
|---|---|

Reporting group description:

Participants received 3 intravenous (IV) loading doses of 200 mg of isavuconazole on days 1 and 2, followed by an IV maintenance dose of 200 mg once daily from day 3 to day 56. On day 11 at the discretion of the investigator, non-neutropenic participants could switch from IV to oral therapy. Oral therapy consisted of 200 mg isavuconazole once daily.

| Reporting group title | Caspofungin (CAS)/Voriconazole |
|---|---|

Reporting group description:

Participants received 1 intravenous (IV) loading dose of 70 mg CAS on day 1, followed by an IV maintenance dose of 50 mg CAS from day 2 to day 56. On day 11 at the discretion of the investigator, non-neutropenic participants could switch from IV CAS to oral voriconazole comprising of a loading dose of 400 mg twice daily (BID) on the first day of oral therapy followed by standard dosing of 200 mg BID thereafter.

| Subject analysis set title | Intent to Treat (ITT) |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The intent to treat (ITT) population consisted of all randomized participants who received at least one dose of study drug. For the ITT, data were analyzed by the treatment group that participants were randomized to.

| Subject analysis set title | Modified Intent to Treat (mITT) |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The modified intent to treat (mITT) population consisted of ITT participants who had documented invasive candidiasis or candidemia at baseline based on the assessment of the independent blinded Data Review Committee (DRC).

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

Subject analysis set description:

The safety analysis set (SAF) consisted of all participants who received at least one dose of study drug. For the SAF data were analyzed according to the first dose of study drug participants received even if it was different from what they were randomized to.

### Primary: Percentage of Participants with Overall Response of Success at the End of Intravenous Therapy (EOIV) as Determined by the Data Review Committee (DRC) Based on the Assessments of Clinical and Mycological Responses as well as alternative systemic AFT use

| End point title | Percentage of Participants with Overall Response of Success at the End of Intravenous Therapy (EOIV) as Determined by the Data Review Committee (DRC) Based on the Assessments of Clinical and Mycological Responses as well as alternative systemic AFT use |
|---|---|

End point description:

A Data Review Committee (DRC) was established from independent experts in the field of fungal infections to determine diagnosis and outcomes independently of the investigators and sponsor [Crude rates of overall response were calculated within treatment group]. Success was defined as clinical response (complete or partial) and mycological response (eradication or presumed eradication), without the use of alternative systemic antifungal therapy (AFT) within 48 hours after the last dose of IV study medication. The isavuconazole and caspofungin group included participants who switched to oral isavuconazole and oral voriconazole. The mITT population was used for this analysis.

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

End point timeframe:

Day 7 and End of Intravenous Therapy (EOIV) (up to 56 days)

| End point values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Success | 60.3 | 71.1 | | |

### Statistical analyses

| Statistical analysis title | Adjusted Treatment Difference (ISA-CAS) |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified Cochran-Mantel-Haenszel (CMH) method with the strata of geographical region and baseline neutropenic status. The 95% CI for treatment group is based on a binomial distribution and the 95% CI for the treatment difference is calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Caspofungin (CAS)/Voriconazole v Isavuconazole (ISA) |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -10.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.9 |
| upper limit | -1.8 |

Notes:

[1] - The lower bound of the 95% CI for the adjusted treatment difference was compared to the protocol prespecified NIM value of -15%. If the lower bound were greater than -15%, isavuconazole would be declared as noninferior to caspofungin.

### Secondary: Percentage of Participants with Overall Response of Success at Follow Up Visit 1 (FU1) 2 Weeks After End of Treatment (EOT) as Determined by the DRC Based on the Assessments of Clinical, Mycological Responses and Antifungal Therapy (AFT)

| End point title | Percentage of Participants with Overall Response of Success at Follow Up Visit 1 (FU1) 2 Weeks After End of Treatment (EOT) as Determined by the DRC Based on the Assessments of Clinical, Mycological Responses and Antifungal Therapy (AFT) |
|---|---|

End point description:

A data review committee (DRC) was established from independent experts in the field of fungal infections to determine diagnosis and outcomes independently of the investigators and sponsor. Success was defined based on the DRC assessments of clinical and mycological responses as well as alternative systemic antifungal therapy (AFT) use and recurrent or emergent infection. The isavuconazole and caspofungin group included participants who switched to oral isavuconazol and voriconazole. The mITT population was used for this analysis.

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

End point timeframe:

2 weeks after last dose of study drug

| End point values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Success | 54.8 | 57.2 | | |

### Statistical analyses

| Statistical analysis title | Adjusted Treatment Difference (ISA-CAS) |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -2.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.2 |
| upper limit | 6.8 |

Notes:

[2] - If the noninferiority for the primary efficacy endpoint were met, the noninferiority for the key secondary endpoint would be established if
the lower limit of the 95% CI were greater than -15%.

### Secondary: Percentage of Participants with Overall Response of Success at EOT and Follow Up Visit 2 (FU2) as Determined by the DRC Based on the Assessments of Clinical and Mycological Responses as well as alternative systemic AFT use at EOT and FU2

| End point title | Percentage of Participants with Overall Response of Success at EOT and Follow Up Visit 2 (FU2) as Determined by the DRC Based on the Assessments of Clinical and Mycological Responses as well as alternative systemic AFT use at EOT and FU2 |
|---|---|

End point description:

A data review committee (DRC) was established from independent experts in the field of fungal infections to determine diagnosis and outcomes independently of the investigators and sponsor. Success was defined as clinical response (complete or partial) and mycological response (eradication or presumed eradication), without the use of alternative systemic AFT within 48 hours after the last dose of IV study medication (for EOT analysis) or for continued treatment of the primary infection, or for recurrent or emergent infection by FU2, with no recurrent or emergent infection by FU2 (for FU2 analysis). N= represents actual number of participants used in the analysis. The mITT population was used for this analysis.

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

End point timeframe:

EOT (up to Day 56) and FU2 (6 weeks after last dose of study drug)

| **End point values** | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| EOT [N=122; 145] | 61.3 | 72.1 | | |
| FU2 [N=86; 97] | 43.2 | 48.3 | | |

**Statistical analyses**

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [EOT] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference % |
| Point estimate | -10.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.9 |
| upper limit | -1.9 |

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [FU2] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference % |
| Point estimate | -5.4 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -15 |
| upper limit | 4.2 |

## Secondary: Percentage of Participants with Clinical Response of Success at EOIV, EOT, FU1 and FU2 as Determined by the Data Review Committee (DRC)

| End point title | Percentage of Participants with Clinical Response of Success at EOIV, EOT, FU1 and FU2 as Determined by the Data Review Committee (DRC) |
|---|---|

End point description:

A data review committee (DRC) was established from independent experts in the field of fungal infections to determine diagnosis and outcomes independently of the investigators and sponsor. Success was defined as clinical response (complete or partial). The isavuconazole and caspofungin group included participants who switched to oral isavuconazol and voriconazole. The mITT population was used for this analysis.

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

End point timeframe:

EOIV, EOT (up to Day 56) and 2 weeks after last dose of study drug and 6 weeks after last dose of study drug

| **End point values** | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Success- End of Intravenous Treatment (EOIV) | 76.4 | 84.1 | | |
| Success- End of Treatment (EOT) | 76.4 | 84.6 | | |
| Success- Follow-up Visit 1 (FU1) | 67.8 | 67.7 | | |
| Success- Follow-up Visit 2 (FU2) | 52.8 | 58.2 | | |

### Statistical analyses

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [EOIV] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was
calculated based on a normal approximation.

| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -8.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.4 |
| upper limit | -0.9 |

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [EOT] |
|---|---|

Statistical analysis description:

TThe adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -8.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.8 |
| upper limit | -1.5 |

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [FU1] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.1 |
| upper limit | 8.3 |

| Statistical analysis title | Adjusted Treatment Difference (ISA-CAS) [FU2] |
|---|---|

Statistical analysis description:

TThe adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -5.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.3 |
| upper limit | 3.6 |

## Secondary: Percentage of Participants with Mycological Response of Success at EOIV, EOT, FU1 and FU2 as Determined by the Data Review Committee (DRC)

| End point title | Percentage of Participants with Mycological Response of Success at EOIV, EOT, FU1 and FU2 as Determined by the Data Review Committee (DRC) |
|---|---|

End point description:

A data review committee (DRC) was established from independent experts in the field of fungal infections to determine diagnosis and outcomes independently of the investigators and sponsor. Success was defined as mycological response (Eradication or Presumed Eradication). The isavuconazole and caspofungin group included participants who switched to oral isavuconazol and voriconazole. The mITT population was used for this analysis.

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

End point timeframe:

EOIV (up to the maximum duration of therapy of 56 days), EOT (up to day 56), 2 weeks after last dose of study drug, and 6 weeks after last dose of study drug

| End point values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Success-EOIV | 70.9 | 85.6 | | |
| Success-EOT | 71.9 | 87.6 | | |
| Success-FU1 | 66.8 | 65.7 | | |
| Success-FU2 | 51.8 | 56.7 | | |

## Statistical analyses

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [EOIV] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -14.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.7 |
| upper limit | -7 |

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [EOT] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was
calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -15.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.5 |
| upper limit | -8.4 |

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [FU1] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |

| | |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.1 |
| upper limit | 9.6 |

| **Statistical analysis title** | Adjusted Treatment Difference (ISA-CAS) [FU2] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -5.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.7 |
| upper limit | 4.3 |

## Secondary: Percentage of Participants with Mycological Response of Success at Day 7 and EOT as Determined by The Investigator

| End point title | Percentage of Participants with Mycological Response of Success at Day 7 and EOT as Determined by The Investigator |
|---|---|

End point description:

The isavuconazole and caspofungin group included participants who switched to oral isavuconazol and voriconazole.Success was defined as mycological response (Eradication or Presumed Eradication). The mITT population was used for this analysis.

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

End point timeframe:

Day 7 and EOT (up to Day 56)

| End point values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Day 7 | 61.3 | 72.1 | | |
| EOT | 72.9 | 81.1 | | |

## Statistical analyses

| Statistical analysis title | Adjusted Treatment Difference (ISA-CAS) [EOT] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -8.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.5 |
| upper limit | -0.4 |

| Statistical analysis title | Adjusted Treatment Difference (ISA-CAS) [Day 7] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -11.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.4 |
| upper limit | -2.5 |

## Secondary: Percentage of Participants with Clinical Response of Success at Day 7 and EOT as Determined by The Investigator

| End point title | Percentage of Participants with Clinical Response of Success at Day 7 and EOT as Determined by The Investigator |
|---|---|

End point description:

The isavuconazole and caspofungin group included participants who switched to oral isavuconazol and voriconazole. Success was defined as clinical response (complete or partial). The mITT population was used for this analysis.

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

End point timeframe:

Day 7 and EOT (up to Day 56)

| End point values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Day 7 | 54.3 | 64.7 | | |
| EOT | 70.9 | 78.6 | | |

### Statistical analyses

| Statistical analysis title | Adjusted Treatment Difference (ISA-CAS) [Day 7] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was calculated based on a normal approximation.

| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Difference (%) |
| Point estimate | -11.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.3 |
| upper limit | -1.9 |

| Statistical analysis title | Adjusted Treatment Difference (ISA-CAS) [EOT] |
|---|---|

Statistical analysis description:

The adjusted treatment difference (ISA-CAS) was calculated by a stratified CMH method with the strata of geographical region and baseline neutropenic status. The 95% CI for the adjusted treatment difference was

calculated based on a normal approximation.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | -8.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.3 |
| upper limit | 0.1 |

## Secondary: All-Cause Mortality (ACM) at Day 14 and Day 56

| | |
|---|---|
| End point title | All-Cause Mortality (ACM) at Day 14 and Day 56 |

End point description:

All-cause mortality is represented as the percentage of participants who died on or before the landmark day as well as participants who were lost to follow-up (i.e., unknown survival status) before the analysis day were counted as death. All-cause mortality rate was examined at day 14 and day 56. The mITT population was used for this analysis.

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

End point timeframe:

Day 14 and Day 56

| End point values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 199 | 201 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Day 14 All-cause Mortality | 14.6 | 12.4 | | |
| Day 56 All-cause Mortality | 30.7 | 29.9 | | |

## Statistical analyses

| Statistical analysis title | All-cause Mortality - Day 56 |
|---|---|

Statistical analysis description:

Adjusted treatment difference (Isavuconazole-Caspofungin) is calculated by a stratified CMH method with the strata of geographical regions, and baseline neutropenic status. The 95% CI for treatment group is based on a binomial distribution and the 95% CI for the treatment difference is calculated based on a normal approximation.The ITT population was used for this analysis.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |

| | |
|---|---|
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.1 |
| upper limit | 10 |

| **Statistical analysis title** | All-cause Mortality - Day 14 |
|---|---|

Statistical analysis description:

Adjusted treatment difference (Isavuconazole-Caspofungin) is calculated by a stratified CMH method with the strata of geographical regions, and baseline neutropenic status. The 95% CI for treatment group is based on a binomial distribution and the 95% CI for the treatment difference is calculated based on a normal approximation. The ITT population was used for this analysis.

| | |
|---|---|
| Comparison groups | Isavuconazole (ISA) v Caspofungin (CAS)/Voriconazole |
| Number of subjects included in analysis | 400 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Adjusted Treatment Difference (%) |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8 |
| upper limit | 8.9 |

## Secondary: Time to First Confirmed Negative Culture

| End point title | Time to First Confirmed Negative Culture |
|---|---|

End point description:

The first confirmed negative blood culture was defined as the first negative blood culture on or after first dose followed by a second negative blood culture at least 24 hours apart without any positive blood cultures in between. A participant without a confirmed negative blood culture was censored on the participant's last visit day. This endpoint was analyzed for mITT participants with candidemia only using the Kaplan-Meier method. Only participants with at least one positive blood culture on or prior to first dose and the culture not resolved prior to first dose was included in this analysis

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

End point timeframe:

Days 3, 7, 10, 14 and 21

| End point values | Isavuconazole (ISA) | Caspofungin (CAS)/Voriconazole | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 119 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 4 (3 to 6) | 3 (3 to 4) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 - Day 56 + FU2 (1 Week)

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAE) is an adverse event which has started after first study drug administration until 28 days after the last dose of study drug.

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

### Dictionary used

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

### Reporting groups

| | |
|---|---|
| Reporting group title | Caspofungin (CAS)/Voriconazole |

Reporting group description:

Participants received 1 intravenous (IV) loading dose of 70 mg CAS on day 1, followed by an IV maintenance dose of 50 mg CAS from day 2 to day 56. On day 11 at the discretion of the investigator, non-neutropenic participants could switch from IV CAS to oral voriconazole comprising of a loading dose of 400 mg twice daily (BID) on the first day of oral therapy followed by standard dosing of 200 mg BID thereafter.

| | |
|---|---|
| Reporting group title | Isavuconazole (ISA) |

Reporting group description:

Participants received 3 intravenous (IV) loading doses of 200 mg of isavuconazole on days 1 and 2, followed by an IV maintenance dose of 200 mg once daily from day 3 to day 56. On day 11 at the discretion of the investigator, non-neutropenic patients could switch from IV to oral therapy. Oral therapy consisted of 200 mg isavuconazole once daily.

| Serious adverse events | Caspofungin (CAS)/Voriconazole | Isavuconazole (ISA) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 106 / 220 (48.18%) | 112 / 220 (50.91%) | |
| number of deaths (all causes) | 68 | 66 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia recurrent | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hodgkin's disease refractory | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lymphoma | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neoplasm progression | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pancreatic carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sarcoma | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Thyroid neoplasm | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Arterial thrombosis limb | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemodynamic instability | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 3 / 220 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Drug withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 7 / 220 (3.18%) | 5 / 220 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 5 | 1 / 3 | |
| Necrosis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 3 / 220 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pulmonary alveolar haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 4 / 220 (1.82%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Pulmonary necrosis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 5 / 220 (2.27%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Respiratory failure | | | |
| subjects affected / exposed | 8 / 220 (3.64%) | 12 / 220 (5.45%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 13 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 5 | |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme abnormal | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 3 / 220 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Brain herniation | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Donor site complication | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug toxicity | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial bones fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subcutaneous haematoma | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound haemorrhage | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Sickle cell anaemia with crisis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Arrest | | | |
| subjects affected / exposed | 6 / 220 (2.73%) | 4 / 220 (1.82%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | |
| Cardiac Failure | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypertensive heart disease | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sick sinus syndrome | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Torsade de pointes | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Basilar artery thrombosis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemic encephalopathy | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypoxic encephalopathy | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intracranial haematoma | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasogenic cerebral oedema | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (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 | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 220 (1.36%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia Hemolytic Autoimmune | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

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|---|---|---|---|
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal perforation | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocutaneous fistula | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 220 (1.36%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatosplenomegaly | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

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|---|---|---|---|
| Nephrectasia | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive uropathy | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Renal failure acute | | | |
| subjects affected / exposed | 3 / 220 (1.36%) | 10 / 220 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 10 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | |
| Renal failure chronic | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Diabetes insipidus | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (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 | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Fistula | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| 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 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 3 / 220 (1.36%) | |
| 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 | 4 / 220 (1.82%) | 3 / 220 (1.36%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Candida endophthalmitis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter related infection | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cellulitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral aspergillosis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (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 | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterobacter sepsis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Klebsiella infection | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Mediastinitis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 220 (2.73%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 9 / 220 (4.09%) | 16 / 220 (7.27%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 8 | |
| Septic shock | | | |
| subjects affected / exposed | 11 / 220 (5.00%) | 19 / 220 (8.64%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 19 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 12 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (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 | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic candida | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 220 (0.45%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection enterococcal | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 220 (0.91%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Wound abscess | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Metabolism and nutrition disorders** | | | |
| Diabetic complication | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| 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 / 220 (0.45%) | 0 / 220 (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 | 3 / 220 (1.36%) | 2 / 220 (0.91%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 220 (0.45%) | 0 / 220 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 0 / 220 (0.00%) | 1 / 220 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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

| **Non-serious adverse events** | Caspofungin (CAS)/Voriconazole | Isavuconazole (ISA) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 167 / 220 (75.91%) | 162 / 220 (73.64%) | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 11 / 220 (5.00%) | 4 / 220 (1.82%) | |
| occurrences (all) | 12 | 4 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 11 / 220 (5.00%) | 5 / 220 (2.27%) | |
| occurrences (all) | 11 | 5 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 220 (5.45%) | 9 / 220 (4.09%) | |
| occurrences (all) | 13 | 9 | |
| Hypotension | | | |
| subjects affected / exposed | 27 / 220 (12.27%) | 22 / 220 (10.00%) | |
| occurrences (all) | 29 | 30 | |
| Phlebitis | | | |
| subjects affected / exposed | 15 / 220 (6.82%) | 14 / 220 (6.36%) | |
| occurrences (all) | 20 | 14 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 9 / 220 (4.09%) | 18 / 220 (8.18%) | |
| occurrences (all) | 10 | 20 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 18 / 220 (8.18%) | 13 / 220 (5.91%) | |
| occurrences (all) | 21 | 14 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 6 / 220 (2.73%) | 11 / 220 (5.00%) | |
| occurrences (all) | 6 | 15 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 220 (7.27%) | 15 / 220 (6.82%) | |
| occurrences (all) | 17 | 17 | |
| Pyrexia | | | |
| subjects affected / exposed | 41 / 220 (18.64%) | 38 / 220 (17.27%) | |
| occurrences (all) | 73 | 56 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 20 / 220 (9.09%) | 16 / 220 (7.27%) | |
| occurrences (all) | 23 | 17 | |
| Constipation | | | |
| subjects affected / exposed | 24 / 220 (10.91%) | 32 / 220 (14.55%) | |
| occurrences (all) | 31 | 34 | |
| Diarrhoea | | | |
| subjects affected / exposed | 41 / 220 (18.64%) | 33 / 220 (15.00%) | |
| occurrences (all) | 49 | 37 | |
| Nausea | | | |
| subjects affected / exposed | 30 / 220 (13.64%) | 21 / 220 (9.55%) | |
| occurrences (all) | 37 | 28 | |
| Vomiting | | | |
| subjects affected / exposed | 37 / 220 (16.82%) | 33 / 220 (15.00%) | |
| occurrences (all) | 49 | 44 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 13 / 220 (5.91%) | 10 / 220 (4.55%) | |
| occurrences (all) | 14 | 11 | |
| Dyspnoea | | | |
| subjects affected / exposed | 14 / 220 (6.36%) | 15 / 220 (6.82%) | |
| occurrences (all) | 14 | 18 | |

| | | | |
|---|---|---|---|
| Pleural effusion | | | |
| subjects affected / exposed | 12 / 220 (5.45%) | 11 / 220 (5.00%) | |
| occurrences (all) | 12 | 11 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 10 / 220 (4.55%) | 14 / 220 (6.36%) | |
| occurrences (all) | 19 | 15 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 13 / 220 (5.91%) | 5 / 220 (2.27%) | |
| occurrences (all) | 15 | 5 | |
| Anxiety | | | |
| subjects affected / exposed | 7 / 220 (3.18%) | 11 / 220 (5.00%) | |
| occurrences (all) | 8 | 11 | |
| Insomnia | | | |
| subjects affected / exposed | 10 / 220 (4.55%) | 12 / 220 (5.45%) | |
| occurrences (all) | 10 | 13 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 6 / 220 (2.73%) | 13 / 220 (5.91%) | |
| occurrences (all) | 6 | 15 | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 9 / 220 (4.09%) | 11 / 220 (5.00%) | |
| occurrences (all) | 9 | 12 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 9 / 220 (4.09%) | 13 / 220 (5.91%) | |
| occurrences (all) | 10 | 13 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 12 / 220 (5.45%) | 7 / 220 (3.18%) | |
| occurrences (all) | 12 | 7 | |
| Metabolism and nutrition disorders | | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 18 / 220 (8.18%) | 18 / 220 (8.18%) | |
| occurrences (all) | 21 | 19 | |
| Hypomagnesaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 29 / 220 (13.18%) | 18 / 220 (8.18%) | |
| occurrences (all) | 31 | 22 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 44 / 220 (20.00%) | 41 / 220 (18.64%) | |
| occurrences (all) | 50 | 49 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 14 / 220 (6.36%) | 12 / 220 (5.45%) | |
| occurrences (all) | 16 | 12 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 9 / 220 (4.09%) | 15 / 220 (6.82%) | |
| occurrences (all) | 11 | 15 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 09 January 2007 | Protocol Amendment 1, dated January 09, 2007, changed the study drug name from BAL4815 to isavuconazole. The number of study sites was increased from 100 to 180. The inclusion/exclusion criteria were amended and further clarified. The timing of the first oral maintenance dose was clarified. The use of 70 mg caspofungin was clarified. The setting of treatment administration after the first 48 hours was specified. The number of plasma samples for pharmacokinetic profiling was reduced from 8 to 7. The measures taken to prevent unblinding of the IDMSB were specified. The information on drug-drug interactions in healthy volunteers was updated. The list of concomitant medications that should be used with caution was updated. The time windows for visits starting at day 7 were amended. A statement was added that in case of cultures with voriconazole- or caspofungin-resistant species during the study period, patients were allowed to remain in the study provided they showed clinical improvement; otherwise, they would be considered failures and withdrawn from the study. |
| 12 February 2007 | Protocol Amendment 2, dated February 12, 2007, amended and further clarified the inclusion/exclusion criteria. The dose of 70 mg caspofungin was clarified to be a maintenance dose for patients receiving concomitant efavirenz, nevirapine, dexamethasone or phenytoin (in addition to patients with a body weight > 80 kg). A prohibition on switching patients from oral therapy back to intravenous therapy was added. Isolate re-evaluation in a central laboratory was limited to specific positive cultures. Dose adaptation of caspofungin was allowed. The interval between IV infusions of isavuconazole and caspofungin was amended to 8 hours. The schedule of assessments was updated with a blood sample collection for biomarkers and a footnote specifying the day for pharmacokinetic assessments. The site's informed consent log was added. Circumstances for analyzing the biomarker sample were specified. Day 14 was specified as the preferred day for pharmacokinetic sample collection. Reporting of serious adverse events (SAEs) in patients who were consented but not randomized was clarified. The interim analysis text was updated. |
| 07 April 2008 | Protocol Amendment 3, dated April 7, 2008, amended and exclusion criterion 11 was revised to exclude patients who received more than 48 hours of prior systemic AFT within 96 hours prior to randomization. |
| 27 May 2010 | Protocol Amendment 4, dated May 27, 2010, reflected the change in study sponsorship; Basilea Pharmaceuticals was replaced with Astellas Pharma Global Development, Inc.The inclusion/exclusion criteria were amended and further clarified. Secondary and exploratory efficacy variables were added. Isavuconazole dosing was clarified. Criteria were added to extend therapy if needed for deep-seated infections. Additional medications were added to the list of prohibited concomitant medications or the list of concomitant medications to be used with caution. Patient withdrawal criteria were clarified. Study procedures were amended, clarified and added. The collection of trough samples and pharmacokinetic samples was specified. The statistical power, sample size, type I and type II error were clarified. The P value for evidence of superiority of isavuconazole was amended. The safety population criteria were amended. The pharmacokinetic population was amended and the pharmacokinetic analysis was updated. |

| | |
|---|---|
| 17 November 2010 | Protocol Amendment 5, dated November 17, 2010, updated the primary study variable and amended the secondary objective and the exploratory objectives and variables. The interim analysis was omitted from the protocol because it was not a requirement and the IDSMB's ongoing review of blinded safety data ensured the continuing safety of patients. The inclusion/exclusion criteria were amended and further clarified. The timing of the first IV maintenance dose was clarified. The collection times of pharmacokinetic trough samples were amended. The number of patients included in IDSMB review was corrected. Guidance to determine neutropenia resolution and additional guidance for oral therapy dosing were provided. Follow-up visit 3 and biomarker sampling were removed. Laboratory tests were added and creatinine clearance calculation was amended. |
| 15 July 2013 | Protocol Amendment 6, dated July 15, 2013, amended the primary study objective of the study to assess the efficacy of treatment with isavuconazole vs caspofungin instead of comparing the efficacy of isavuconazole vs caspofungin and voriconazole. The primary efficacy variable was amended to overall response at EOIV instead of overall response at FU1. Protocol Amendment 6 further amended the secondary study objectives and the secondary efficacy variables and implemented a DRC. The statistical power, sample size, type I and type II error were amended and the justification for the sample size was included. The inclusion/exclusion criteria were amended and further clarified. The safety and pharmacokinetic variables were amended and further clarified. The collection of pharmacokinetic trough samples was clarified. Sample collection and analysis for the pharmacokinetic sub-study were clarified. The safety analysis was clarified. The requirement for dialysis was removed as a treatment endpoint for this study. More detailed instructions regarding participant counseling and compliance with oral study drug for recording drug accountability were provided. Additional medications were added to the list of prohibited concomitant medications or the list of concomitant medications to be used with caution. The requirement for blood culture sampling through day 9 and the collection of radiology reports were removed. Additional laboratory tests were included. The requirements for electrocardiogram (ECG) collection and the purpose of the central line were clarified. The optional genotype analysis was clarified. |
| 09 September 2014 | Protocol Amendment 8, dated September 09, 2014, reduced the sample size to change the power of the study from 90% to 86%. With the assumption that the overall response rate remained 70% for both arms, a revised sample size of 438 ITT patients (or 350 mITT patients) provided at least 86% power to demonstrate that the non-inferiority of isavuconazole to caspofungin with the chosen noninferiority margin (NIM) of 15%. |

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 March 2011. | 01 March 2011 |

Notes:

## Limitations and caveats

None reported