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	Subject, Investigator

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
Missing	1	-
Adverse event, serious fatal	57	56
Admin/Other	20	14
Consent withdrawn by subject	9	1
Lost to follow-up	14	17

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 Units: Subjects			
Age continuous Units: years			
arithmetic mean	58	57.9	
standard deviation	± 17.54	± 16.88	-
Gender categorical 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			
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	
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	
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	
General disorders and administration site conditions			
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	
Chest discomfort			
subjects affected / exposed	0 / 220 (0.00%)	1 / 220 (0.45%)	
occurrences causally related to	0 / 0	0 / 1	

treatment / all			
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	
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			
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	
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	
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			
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			
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	
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
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	
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 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	
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	
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	
Blood and lymphatic system disorders			
Anaemia			
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	

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			
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	
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			
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			
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			
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	
Renal and urinary disorders			
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	
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	
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	
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	
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	
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	
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	
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	
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	0 / 0	0 / 1	

treatment / all			
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	
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			
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 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	
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	
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	

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%)	
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	
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	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	9 / 220 (4.09%)	18 / 220 (8.18%)	
occurrences (all)	10	20	
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	
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	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 220 (3.18%)	11 / 220 (5.00%)	
occurrences (all)	8	11	
Agitation			
subjects affected / exposed	13 / 220 (5.91%)	5 / 220 (2.27%)	
occurrences (all)	15	5	
Insomnia			
subjects affected / exposed	10 / 220 (4.55%)	12 / 220 (5.45%)	
occurrences (all)	10	13	
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	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	10 / 220 (4.55%)	14 / 220 (6.36%)	
occurrences (all)	19	15	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 220 (2.73%)	13 / 220 (5.91%)	
occurrences (all)	6	15	
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	
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	

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