Clinical trial results:
A Phase 3 Randomized Study of the Efficacy and Safety of Posaconazole versus Voriconazole for the Treatment of Invasive Aspergillosis in Adults and Adolescents (Phase 3; Protocol No. MK-5592-069)

Summary

EudraCT number	2011-003938-14
Trial protocol	ES DE BE LT PT GB EE IT PL GR FR HU CZ HR RO
Global end of trial date	10 September 2019

Results information

Result version number	v1
This version publication date	26 August 2020
First version publication date	26 August 2020

Trial information

Trial identification

Sponsor protocol code	P06200

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01782131
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration: MK-5592-069

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2019
Global end of trial reached?	Yes
Global end of trial date	10 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of posaconazole (POS) versus voriconazole (VOR) in the treatment of adults and adolescents with invasive aspergillosis (IA). The primary hypothesis is that the all-cause mortality through Day 42 in the POS treatment group is non-inferior to that in the VOR treatment group.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2013
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	Belgium: 84
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	China: 62
Country: Number of subjects enrolled	Colombia: 51
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Israel: 59
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Mexico: 29
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 36

Country: Number of subjects enrolled	Serbia: 4
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Turkey: 30
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	585
EEA total number of subjects	172

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)	5
Adults (18-64 years)	417
From 65 to 84 years	161
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After a screening phase of up to 7 days, 585 participants were enrolled/randomized, but only 575 began treatment (288 in the posaconazole [POS] group and 287 in the voriconazole [VOR] group).

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Posaconazole

Arm description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Voriconazole

Arm description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Posaconazole	Voriconazole
Started	293	292
Completed	288	287
Not completed	5	5
Randomized but not treated	5	5

Period 2

Period 2 title	Treatment
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Posaconazole

Arm description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Arm type	Experimental
Investigational medicinal product name	Posaconazole
Investigational medicinal product code	
Other name	SCH 056592 MK-5592 Noxafil®
Pharmaceutical forms	Tablet, Infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

POS IV: Day 1b: 300 mg BID, Day 2-84: 300 mg QD;
POS oral: Day 1b: 300 mg BID, Day 2-84: 300 mg QD

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Matching placebo received for Posaconazole

Arm title	Voriconazole

Arm description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Arm type	Active comparator
Investigational medicinal product name	Voriconazole
Investigational medicinal product code	
Other name	VFEND®
Pharmaceutical forms	Capsule, Infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

VOR IV: Day 1b: 6 mg/kg per body weight administered BID,
Day 2-84: 4 mg/kg per body weight administered BID;
VOR oral: Day 1b: 300 mg BID, Day 2-84: 200 mg BID

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:
Matching placebo received for Voriconazole

Notes:
[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.
Justification: The All Patients as Treated population was used as the baseline population.

Number of subjects in period 2[2]	Posaconazole	Voriconazole
Started	288	287
Completed	184	177
Not completed	104	110
Adverse event, serious fatal	93	96
Consent withdrawn by subject	10	10
Lost to follow-up	1	3
Reason not provided	-	1

Notes:
[2] - 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: The All Patients as Treated population was used as the baseline population.

Baseline characteristics

Reporting groups	
Reporting group title	Posaconazole

Reporting group description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Reporting group title	Voriconazole

Reporting group description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Reporting group values	Posaconazole	Voriconazole	Total
Number of subjects	288	287	575
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	53.5	53.0	
standard deviation	± 16.7	± 15.9	-
Gender Categorical Units: Subjects			
Female	116	115	231
Male	172	172	344
Race Units: Subjects			
American Indian or Alaska Native	4	6	10
Asian	62	60	122
Black or African American	3	4	7
Multiple	25	25	50
White	194	192	386
Ethnicity Units: Subjects			
Hispanic or Latino	48	57	105
Not Hispanic or Latino	220	219	439
Unknown or Not Reported	20	11	31

End points

End points reporting groups

Reporting group title	Posaconazole

Reporting group description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Reporting group title	Voriconazole

Reporting group description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Reporting group title	Posaconazole

Reporting group description:

Participants received 300 mg posaconazole (POS) intravenous (IV) twice per day (BID) on Day 1, and then received 300 mg POS IV plus placebo IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral POS tablets plus oral placebo tablets QD for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Reporting group title	Voriconazole

Reporting group description:

Participants received 6 mg/kg voriconazole (VOR) IV BID on Day 1, and then received 4 mg/kg VOR IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with VOR capsules or VOR placebo capsules BID for up to 12 weeks of treatment. Most participants were expected to initiate treatment with IV therapy and transition to oral therapy as clinically indicated, with some participants initiating treatment with oral therapy, per clinical judgment.

Primary: Percentage of Participants Who Died Through Day 42 in the Intention to Treat Population

End point title	Percentage of Participants Who Died Through Day 42 in the Intention to Treat Population

End point description:

The percentage of participants who died with posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) in the Intention to Treat (ITT) population through Day 42 was assessed. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Primary

End point timeframe:

Up to ~42 days

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)	15.3	20.6		

Statistical analyses

Statistical analysis title	All-Cause Mortality by Day 42 in ITT

Statistical analysis description:

Based on Miettinen and Nurminen's method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme. The p-Value is based on the one-sided non inferiority test. Non-inferiority of posaconazole vs. voriconazole is established if the upper limit of the 95% confidence interval is less than 10%.

Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Miettinen and Nurminen
Parameter estimate	Estimated Difference in Percent
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.6
upper limit	1

Secondary: Percentage of Participants Who Died Through Day 42 in the Full Analysis Set Population

End point title	Percentage of Participants Who Died Through Day 42 in the Full Analysis Set Population

End point description:

The percentage of participants who died with POS compared to VOR in the first line treatment of invasive aspergillosis (IA) in the Full Analysis Set (FAS) population through Day 42 was assessed. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions) and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to ~42 days

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	171		
Units: Percentage of Participants				
number (not applicable)	19.0	18.7		

Statistical analyses

Statistical analysis title	All-Cause Mortality by Day 42 in FAS

Statistical analysis description:

Based on Miettinen and Nurminen’s method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.

Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in Percent
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	8.8

Secondary: Percentage of Participants Who Died Through Day 84 in the ITT Population

End point title	Percentage of Participants Who Died Through Day 84 in the ITT Population

End point description:

The percentage of participants who died with posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) in the ITT population through Day 84 was assessed. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to ~84 days

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)	28.1	30.7		

Statistical analyses

Statistical analysis title	All-Cause Mortality by Day 84 in ITT

Statistical analysis description:

Based on Miettinen and Nurminen’s method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.

Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in Percent
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	4.9

Secondary: Percentage of Participants Who Died Through Day 84 in the FAS Population

End point title	Percentage of Participants Who Died Through Day 84 in the FAS Population

End point description:

The percentage of participants who died with POS compared to VOR in the first line treatment of invasive aspergillosis (IA) in the FAS population through Day 84 was assessed. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions) and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to ~84 days

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	171		
Units: Percentage of Participants				
number (not applicable)	34.4	31.0		

Statistical analyses

Statistical analysis title	All-Cause Mortality by Day 84 in FAS
Statistical analysis description:	
Based on Miettinen and Nurminen’s method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.	
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percent
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	13.1

Secondary: Percentage of Participants Achieving Global Clinical Response at Week 12 in the FAS Population

End point title	Percentage of Participants Achieving Global Clinical Response at Week 12 in the FAS Population

End point description:

The global clinical response of posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) was assessed. The percentage of participants achieving adjudicated complete and partial global clinical response at Week 12 was reported. Complete response was classified as survival with resolution of fungal disease evidence; Partial response was survival and improvement of fungal disease. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG] definitions) and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to 12 weeks (± 4 weeks)

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	171		
Units: Percentage of Participants				
number (not applicable)	42.3	46.2		

Statistical analyses

Statistical analysis title	Global Clinical Response at Week 12 in FAS

Statistical analysis description:

Based on Miettinen and Nurminen’s method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.

Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in Percent
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.9
upper limit	7.1

Secondary: Percentage of Participants Achieving Global Clinical Response at Week 6 in the FAS Population

End point title	Percentage of Participants Achieving Global Clinical Response at Week 6 in the FAS Population

End point description:

The global clinical response of posaconazole (POS) compared to voriconazole (VOR) in the first line treatment of invasive aspergillosis (IA) was assessed. The percentage of participants achieving adjudicated complete and partial global clinical response at Week 6 was reported. Complete response was classified as survival with resolution of fungal disease evidence; Partial response was survival and improvement of fungal disease. The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group [EORTC/MSG] definitions) and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to 6 weeks (± 2 weeks)

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	171		
Units: Percentage of Participants				
number (not applicable)	44.8	45.6		

Statistical analyses

Statistical analysis title	Global Clinical Response at Week 6 in FAS

Statistical analysis description:

Based on Miettinen and Nurminen’s method stratified by the risk for mortality/poor outcome (high risk, not high risk) and using Cochran-Mantel-Haenszel weighting scheme.

Comparison groups	Posaconazole v Voriconazole

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in Percent
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	10.1

Secondary: Time to Death, All Causes (Kaplan-Meier Estimate of Number of Participants Experiencing a Qualifying Event) in the FAS Population

End point title	Time to Death, All Causes (Kaplan-Meier Estimate of Number of Participants Experiencing a Qualifying Event) in the FAS Population

End point description:

The time to death (all causes) in participants with proven or probable IA receiving POS versus VOR was assessed at Day 114. The Kaplan-Meier estimate reports the number of participants who experienced death (all causes) through Day 114 or ~16 weeks. Participants who did not have any endpoint event until last visit or who were lost to follow-up and had no event were censored at the time of last available information (last study visit). For Day 42 and Day 84, missing or 'unable to determine' responses were considered as failures (dead). The analysis population consisted of all randomized participants who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions) and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to ~16 weeks (± 2 weeks)

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	171		
Units: Participants				
number (not applicable)				
Day 42 (missing responses were included as dead)	31	32		
Day 84 (missing responses were included as dead)	56	53		
Day 114	64	56		

Statistical analyses

Statistical analysis title	Time to Death, All Causes
Comparison groups	Posaconazole v Voriconazole

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.2767 [2]
Method	Kaplan-Meier
Parameter estimate	Survival Rate in Percent
Point estimate	60.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	52.8
upper limit	67.8

Notes:

[1] - From product-limit (Kaplan-Meier) method for censored data.

[2] - Based on Stratified Log-Rank method stratified by the risk for mortality/poor outcome (high risk, not high risk).

Secondary: Number of Participants Who Died Due to Invasive Aspergillosis Through Day 42 in the FAS Population

End point title	Number of Participants Who Died Due to Invasive Aspergillosis Through Day 42 in the FAS Population

End point description:

The number of participants who died due to IA receiving POS versus VOR through Day 42 was assessed. The analysis population consisted of all randomized participants who died by Day 42 and who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions), and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to 42 days

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	32		
Units: Participants				
number (not applicable)	16	10		

Statistical analyses

Statistical analysis title	Died due to IA by Day 42 in FAS

Statistical analysis description:

Based on Miettinen and Nurminen’s method.

Comparison groups	Posaconazole v Voriconazole

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percent
Point estimate	20.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	42.7

Secondary: Number of Participants Who Died Due to Invasive Aspergillosis Through Day 84 in the FAS Population

End point title	Number of Participants Who Died Due to Invasive Aspergillosis Through Day 84 in the FAS Population

End point description:

The number of participants who died due to IA receiving POS versus VOR in the FAS population through Day 84 was assessed. The analysis population consisted of all randomized participants who died by Day 84 and who have been classified as having proven or probable IA (based upon independent adjudication assessment using the modified 2008 European Organization for Research and Treatment of Cancer/Mycoses study group [EORTC/MSG] definitions), and received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Up to 84 days

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	50		
Units: Participants				
number (not applicable)	22	14		

Statistical analyses

Statistical analysis title	Died due to IA by Day 84 in FAS

Statistical analysis description:

Based on Miettinen and Nurminen’s method.

Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percent
Point estimate	11.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	28.6

Secondary: Percentage of Participants with Tier 1 Treatment Emergent Adverse Events

End point title	Percentage of Participants with Tier 1 Treatment Emergent Adverse Events

End point description:

The percentage of participants with Tier 1 treatment-emergent adverse events (TEAEs) was determined. The Tier 1 TEAEs included hepatic safety (elevated aspartate serum transaminase [AST] or alanine serum transaminase [ALT] value ≥3x upper limit of normal (ULN) and an elevated total bilirubin value ≥2x ULN and, at the same time, an alkaline phosphatase value <2 ULN); central nervous system (CNS) and visual disturbances (eye disorders, nervous system disorders, psychiatric disorders), dermatologic reactions, and adrenal insufficiency or temporally associated TEAEs of hypotension. The analysis population consisted of all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to ~16 weeks (± 2 weeks)

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)				
Abnormal Hepatic Laboratory Value	3.8	3.5		
CNS and Visual Disturbances	32.3	35.9		
Dermatologic Reactions	16.3	19.2		
Adrenal Insufficiency or Temporal Hypotension	8.0	7.0		

Statistical analyses

Statistical analysis title	Abnormal Hepatic Laboratory Value
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8305
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	3.6

Statistical analysis title	CNS and Visual Disturbances
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3633
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	4.2

Statistical analysis title	Dermatologic Reactions
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3724
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	3.4

Statistical analysis title	Adrenal Insufficiency or Temporal Hypotension
Comparison groups	Posaconazole v Voriconazole

Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6431
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	5.5

Secondary: Percentage of Participants with at Least One Adverse Event

End point title	Percentage of Participants with at Least One Adverse Event

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to ~16 weeks (± 2 weeks)

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)	97.6	97.6		

Statistical analyses

Statistical analysis title	One or More Adverse Events
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	2.8

Secondary: Percentage of Participants with at Least One Drug Related Adverse Event

End point title	Percentage of Participants with at Least One Drug Related Adverse Event

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to ~16 weeks (± 2 weeks)

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)	29.9	40.1		

Statistical analyses

Statistical analysis title	Drug-Related Adverse Events
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	-10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.9
upper limit	-2.4

Secondary: Percentage of Participants with at Least One Serious Adverse Event

End point title	Percentage of Participants with at Least One Serious Adverse Event

End point description:

A serious adverse event (SAE) was an AE that resulted in death, was life threatening, required or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was another important medical event deemed such by medical or scientific judgment. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to ~16 weeks (± 2 weeks)

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)	61.8	59.9		

Statistical analyses

Statistical analysis title	Serious Adverse Events
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	9.8

Secondary: Percentage of Participants with at Least One Serious Drug-Related Adverse Event

End point title	Percentage of Participants with at Least One Serious Drug-Related Adverse Event

End point description:

An SAE was an AE that resulted in death, was life threatening, required or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was another important medical event deemed such by medical or scientific judgment. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:	
Up to ~16 weeks (± 2 weeks)	

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)	5.6	7.0		

Statistical analyses

Statistical analysis title	Serious Drug-Related Adverse Events
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	2.7

Secondary: Percentage of Participants who Discontinued Study Treatment due to an Adverse Event

End point title	Percentage of Participants who Discontinued Study Treatment due to an Adverse Event

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to ~12 weeks

End point values	Posaconazole	Voriconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	287		
Units: Percentage of Participants				
number (not applicable)	32.3	35.5		

Statistical analyses

Statistical analysis title	Discontinued due to an Adverse Event
Comparison groups	Posaconazole v Voriconazole
Number of subjects included in analysis	575
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percent
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	4.5

Secondary: Steady State Average Concentration (Cavg) of Posaconazole with Food Intake

End point title	Steady State Average Concentration (Cavg) of Posaconazole with Food Intake[3]

End point description:

The characterization of the pharmacokinetics (PK) parameters of POS was determined from plasma samples taken at steady-state after receiving oral tablet of POS. Steady-state Cavg, where Cavg is defined as area under the concentration time-curve from 0 to 24 hours (AUC0-24hr) divided by the dosing interval. No evaluation of food intake on the VOR capsule was presented. The analysis population consisted of all randomized participants in the POS group only who received at least one dose of study treatment. Per protocol, the VOR group was not included in the analysis population because the food intake evaluation was limited to the POS group.

End point type	Secondary

End point timeframe:

Baseline, and at pre-dose on Day 7, Week 2, Week 4, Week 6, and Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The VOR group was not included in the analysis population because the food intake evaluation was limited to the POS group only.

End point values	Posaconazole			
Subject group type	Reporting group			
Number of subjects analysed	288			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1: N=58	1625 (± 902.9)			

Week 2: N=64	1992 (± 1190)			
Week 4: N=67	1994 (± 956.3)			
Week 6: N=65	2005 (± 1333)			
Week 12: N=49	2169 (± 1255)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to ~16 weeks (± 2 weeks)	
Adverse event reporting additional description: The analysis population consisted of all participants who received at least one dose of study treatment. The analysis population for the all-cause mortality included all randomized participants (n=293, n=292).	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Posaconazole (POS)-300 mg
Reporting group description: Participants received posaconazole intravenously (IV) twice per day (BID) on Day 1, and then received posaconazole IV once per day (QD) starting on Day 2 until clinically stable when participants transitioned to oral posaconazole tablets QD for up to 12 weeks of treatment. Participants with renal insufficiency or without central venous catheter access started with posaconazole oral tablets BID on Day 1, and then QD for up to 12 weeks of treatment.	
Reporting group title	Voriconazole (VOR)-6 mg, 4 mg/200 mg
Reporting group description: Participants received voriconazole IV BID on Day 1, and then received voriconazole IV BID on Day 2 until clinically stable when participants transitioned to oral therapy with voriconazole capsules BID for up to 12 weeks of treatment. Participants with renal insufficiency or without central venous catheter access started treatment with oral voriconazole capsules BID on Day 1, and then BID for up to 12 weeks of treatment.	

Serious adverse events	Posaconazole (POS)-300 mg	Voriconazole (VOR)-6 mg, 4 mg/200 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	178 / 288 (61.81%)	172 / 287 (59.93%)	
number of deaths (all causes)	99	99	
number of deaths resulting from adverse events	0	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	3 / 288 (1.04%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Acute lymphocytic leukaemia recurrent			
subjects affected / exposed	3 / 288 (1.04%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	

Acute myeloid leukaemia			
subjects affected / exposed	7 / 288 (2.43%)	12 / 287 (4.18%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 6	0 / 12	
Acute myeloid leukaemia recurrent			
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma recurrent			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell type acute leukaemia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blast crisis in myelogenous leukaemia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diffuse large B-cell lymphoma refractory			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic cancer			

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Leukaemia recurrent				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lymphocytic leukaemia				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Lymphoma				
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Malignant neoplasm progression				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Myelodysplastic syndrome				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Neuroendocrine tumour of the lung				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (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	0 / 288 (0.00%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 1		
Plasma cell myeloma				

subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Precursor T-lymphoblastic lymphoma/leukaemia refractory			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Primary mediastinal large B-cell lymphoma			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 288 (1.04%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 288 (0.69%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
General physical health deterioration			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypothermia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 288 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oedema			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 288 (2.43%)	5 / 287 (1.74%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute graft versus host disease in skin			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Engraftment syndrome			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	2 / 288 (0.69%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Graft versus host disease in liver			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune reconstitution inflammatory syndrome			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	3 / 288 (1.04%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 288 (0.35%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	4 / 288 (1.39%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hypoxia			
subjects affected / exposed	3 / 288 (1.04%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary cavitation			
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 288 (0.69%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 288 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pulmonary oedema			

subjects affected / exposed	1 / 288 (0.35%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	10 / 288 (3.47%)	7 / 287 (2.44%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 8	0 / 4	
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 288 (1.04%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	3 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 288 (0.69%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
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	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus test positive			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver function test increased				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Neutrophil count decreased				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Transaminases increased				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Injury, poisoning and procedural complications				
Concussion				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hip fracture				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Procedural pneumothorax				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Spinal compression fracture				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Subdural haematoma				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Thoracic vertebral fracture			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Accessory cardiac pathway			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	4 / 288 (1.39%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			

subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (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 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral disorder			

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	1 / 1		
Cerebral haemorrhage				
subjects affected / exposed	2 / 288 (0.69%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 2	0 / 1		
Cerebral infarction				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cerebrovascular accident				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dizziness				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Encephalopathy				
subjects affected / exposed	3 / 288 (1.04%)	5 / 287 (1.74%)		
occurrences causally related to treatment / all	1 / 3	3 / 5		
deaths causally related to treatment / all	0 / 1	1 / 1		
Haemorrhage intracranial				
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 1	0 / 1		
Headache				
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 1	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hypoaesthesia				

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 288 (0.35%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke's encephalopathy			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood disorder			

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	3 / 288 (1.04%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	24 / 288 (8.33%)	21 / 287 (7.32%)	
occurrences causally related to treatment / all	0 / 32	0 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Vision blurred			

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
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	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain				
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain upper				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Colitis				
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diarrhoea				
subjects affected / exposed	1 / 288 (0.35%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 1	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Duodenitis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastric varices haemorrhage				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Gastritis				

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal disorder				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 288 (0.00%)	3 / 287 (1.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 1		
Gastrointestinal hypomotility				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ileus				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Inflammatory bowel disease				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intestinal obstruction				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Melaena				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nausea				

subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Rectal haemorrhage			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	3 / 288 (1.04%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 288 (3.13%)	5 / 287 (1.74%)	
occurrences causally related to treatment / all	1 / 9	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders				
Arthralgia				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Back pain				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Muscle twitching				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Musculoskeletal pain				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Infections and infestations				
Abdominal abscess				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal sepsis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Anal infection				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Appendicitis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Aspergillus infection				
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 2		
Atypical pneumonia				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (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	5 / 288 (1.74%)	3 / 287 (1.05%)		
occurrences causally related to treatment / all	0 / 5	0 / 3		
deaths causally related to treatment / all	0 / 2	0 / 0		
Bacterial pericarditis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bacterial sepsis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Brain abscess				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Bronchopulmonary aspergillosis				
subjects affected / exposed	6 / 288 (2.08%)	6 / 287 (2.09%)		
occurrences causally related to treatment / all	0 / 6	0 / 6		
deaths causally related to treatment / all	0 / 4	0 / 3		
Candida sepsis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Cellulitis				

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cellulitis pharyngeal				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Cerebral aspergillosis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Citrobacter sepsis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Clostridial infection				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Clostridium difficile colitis				
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Clostridium difficile infection				
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 1	0 / 0		
Corona virus infection				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cystitis viral				

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cytomegalovirus infection				
subjects affected / exposed	2 / 288 (0.69%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cytomegalovirus viraemia				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Device related infection				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Device related sepsis				
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Disseminated cytomegaloviral infection				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Diverticulitis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Emphysematous cholecystitis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Endocarditis				

subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Endocarditis bacterial				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Enteritis infectious				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Enterobacter pneumonia				
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Enterobacter sepsis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Enterococcal bacteraemia				
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Enterococcal sepsis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Escherichia bacteraemia				
subjects affected / exposed	3 / 288 (1.04%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 4	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 1		
Escherichia sepsis				

subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Febrile infection				
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Fungal infection				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Gastroenteritis norovirus				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hepatosplenic candidiasis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Herpes zoster				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
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 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Infectious pleural effusion				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Influenza				

subjects affected / exposed	3 / 288 (1.04%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 3	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intervertebral discitis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Klebsiella bacteraemia				
subjects affected / exposed	0 / 288 (0.00%)	3 / 287 (1.05%)		
occurrences causally related to treatment / all	0 / 0	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Klebsiella sepsis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Lower respiratory tract infection bacterial				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Lower respiratory tract infection viral				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Meningitis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Mucormycosis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Muscle abscess				

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia			
subjects affected / exposed	23 / 288 (7.99%)	12 / 287 (4.18%)	
occurrences causally related to treatment / all	0 / 27	0 / 12	
deaths causally related to treatment / all	0 / 4	0 / 3	
Pneumonia bacterial			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia cytomegaloviral			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia fungal			

subjects affected / exposed	1 / 288 (0.35%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pneumonia klebsiella			
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomembranous colitis			
subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mycosis			

subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pulmonary sepsis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pulmonary tuberculosis				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pyelonephritis				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Relapsing fever				
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal graft infection				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory tract infection fungal				
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Sepsis				
subjects affected / exposed	10 / 288 (3.47%)	7 / 287 (2.44%)		
occurrences causally related to treatment / all	0 / 10	0 / 7		
deaths causally related to treatment / all	0 / 4	0 / 4		
Sepsis syndrome				

subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	16 / 288 (5.56%)	16 / 287 (5.57%)	
occurrences causally related to treatment / all	0 / 16	0 / 16	
deaths causally related to treatment / all	0 / 12	0 / 11	
Sinusitis			
subjects affected / exposed	1 / 288 (0.35%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis fungal			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 288 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
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	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urinary tract infection			

subjects affected / exposed	2 / 288 (0.69%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 288 (0.69%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	4 / 288 (1.39%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 287 (0.35%)	
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	1 / 288 (0.35%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Posaconazole (POS)-300 mg	Voriconazole (VOR)-6 mg, 4 mg/200 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	232 / 288 (80.56%)	225 / 287 (78.40%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 288 (9.72%)	23 / 287 (8.01%)	
occurrences (all)	33	25	
Hypotension			
subjects affected / exposed	17 / 288 (5.90%)	19 / 287 (6.62%)	
occurrences (all)	20	25	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	18 / 288 (6.25%)	11 / 287 (3.83%)	
occurrences (all)	19	11	
Chills			
subjects affected / exposed	15 / 288 (5.21%)	8 / 287 (2.79%)	
occurrences (all)	19	8	
Fatigue			
subjects affected / exposed	19 / 288 (6.60%)	7 / 287 (2.44%)	
occurrences (all)	20	8	
Oedema peripheral			

subjects affected / exposed	32 / 288 (11.11%)	24 / 287 (8.36%)	
occurrences (all)	35	27	
Pyrexia			
subjects affected / exposed	75 / 288 (26.04%)	69 / 287 (24.04%)	
occurrences (all)	122	127	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 288 (10.42%)	24 / 287 (8.36%)	
occurrences (all)	32	24	
Dyspnoea			
subjects affected / exposed	27 / 288 (9.38%)	24 / 287 (8.36%)	
occurrences (all)	28	28	
Epistaxis			
subjects affected / exposed	31 / 288 (10.76%)	17 / 287 (5.92%)	
occurrences (all)	34	17	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	8 / 288 (2.78%)	16 / 287 (5.57%)	
occurrences (all)	9	16	
Insomnia			
subjects affected / exposed	18 / 288 (6.25%)	16 / 287 (5.57%)	
occurrences (all)	19	17	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	39 / 288 (13.54%)	34 / 287 (11.85%)	
occurrences (all)	49	46	
Aspartate aminotransferase increased			
subjects affected / exposed	36 / 288 (12.50%)	34 / 287 (11.85%)	
occurrences (all)	46	41	
Blood alkaline phosphatase increased			
subjects affected / exposed	21 / 288 (7.29%)	28 / 287 (9.76%)	
occurrences (all)	23	33	
Blood bilirubin increased			
subjects affected / exposed	24 / 288 (8.33%)	20 / 287 (6.97%)	
occurrences (all)	38	24	
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	13 / 288 (4.51%)	17 / 287 (5.92%)	
occurrences (all)	17	20	
Gamma-glutamyltransferase increased			
subjects affected / exposed	13 / 288 (4.51%)	15 / 287 (5.23%)	
occurrences (all)	15	21	
Platelet count decreased			
subjects affected / exposed	15 / 288 (5.21%)	11 / 287 (3.83%)	
occurrences (all)	21	18	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	11 / 288 (3.82%)	18 / 287 (6.27%)	
occurrences (all)	14	23	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 288 (7.29%)	12 / 287 (4.18%)	
occurrences (all)	22	12	
Headache			
subjects affected / exposed	34 / 288 (11.81%)	24 / 287 (8.36%)	
occurrences (all)	45	29	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 288 (7.99%)	29 / 287 (10.10%)	
occurrences (all)	41	46	
Febrile neutropenia			
subjects affected / exposed	21 / 288 (7.29%)	18 / 287 (6.27%)	
occurrences (all)	24	22	
Thrombocytopenia			
subjects affected / exposed	22 / 288 (7.64%)	17 / 287 (5.92%)	
occurrences (all)	28	23	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 288 (9.38%)	24 / 287 (8.36%)	
occurrences (all)	31	24	
Constipation			

subjects affected / exposed	32 / 288 (11.11%)	23 / 287 (8.01%)	
occurrences (all)	36	26	
Diarrhoea			
subjects affected / exposed	52 / 288 (18.06%)	50 / 287 (17.42%)	
occurrences (all)	66	57	
Nausea			
subjects affected / exposed	65 / 288 (22.57%)	50 / 287 (17.42%)	
occurrences (all)	83	63	
Vomiting			
subjects affected / exposed	52 / 288 (18.06%)	38 / 287 (13.24%)	
occurrences (all)	64	57	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	19 / 288 (6.60%)	22 / 287 (7.67%)	
occurrences (all)	22	32	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 288 (5.90%)	9 / 287 (3.14%)	
occurrences (all)	21	10	
Pain in extremity			
subjects affected / exposed	19 / 288 (6.60%)	13 / 287 (4.53%)	
occurrences (all)	20	15	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	15 / 288 (5.21%)	14 / 287 (4.88%)	
occurrences (all)	17	16	
Pneumonia			
subjects affected / exposed	14 / 288 (4.86%)	15 / 287 (5.23%)	
occurrences (all)	14	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	25 / 288 (8.68%)	14 / 287 (4.88%)	
occurrences (all)	25	15	
Hypocalcaemia			
subjects affected / exposed	15 / 288 (5.21%)	13 / 287 (4.53%)	
occurrences (all)	25	27	

Hypokalaemia			
subjects affected / exposed	78 / 288 (27.08%)	49 / 287 (17.07%)	
occurrences (all)	133	72	
Hypomagnesaemia			
subjects affected / exposed	29 / 288 (10.07%)	18 / 287 (6.27%)	
occurrences (all)	48	20	
Hyponatraemia			
subjects affected / exposed	12 / 288 (4.17%)	19 / 287 (6.62%)	
occurrences (all)	19	26	
Hypophosphataemia			
subjects affected / exposed	22 / 288 (7.64%)	9 / 287 (3.14%)	
occurrences (all)	24	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	Amendment 01: Primary reason for amendment was to clarify and simplify the study drug dosing by treatment arms in regard to the dosing for intravenous (IV) and oral posaconazole and voriconazole.
01 July 2013	Amendment 02: Primary reason for amendment was to exclude participants <18 years of age.
14 January 2015	Amendment 03: Primary reason for amendment was to allow the enrollment of adolescents outside of the EU (ie, in those regions with an approved indication for use of oral POS in the adolescent age population (≥13 years of age).
12 August 2016	Amendment 04: Primary reason for amendment was to change the primary study objective and endpoint of global clinical response at Week 6 (FAS population) to a key secondary study objective and endpoint. The all-cause mortality at Week 6 (ITT population) secondary objective and study endpoint was changed to the primary objective and study endpoint.
22 February 2019	Amendment 05: Primary reason for amendment was to clarify protocol and statistical analyses, including approximate sample size and power calculation, time windows used for assessment, and the elimination of 2 secondary objectives for which data analyses was no longer planned.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported