Clinical trial results:
Prospective, Open-label, Comparative, Multicenter Study of Voriconazole Compared to Itraconazole for the Primary Prophylaxis of Invasive Fungal Infections (IFI) in Subjects with Allogeneic Hematopoietic Stem Cell Transplants (HSCT)

Summary

EudraCT number	2005-002800-40
Trial protocol	GB CZ ES PT GR
Global end of trial date	10 February 2009

Results information

Result version number	v1 (current)
This version publication date	25 May 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	A1501073

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00289991
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc. , 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc. , 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the "Success" of antifungal prophylaxis with voriconazole versus itraconazole at 180 days post transplant. Success was measured using a composite endpoint of: survival to Day 180 with no breakthrough invasive fungal infection and no discontinuation of study drug for more than 14 days during the 100-day prophylaxis period.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 26
Country: Number of subjects enrolled	Spain: 107
Country: Number of subjects enrolled	United Kingdom: 115
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	France: 88
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Jordan: 1
Country: Number of subjects enrolled	Egypt: 18
Country: Number of subjects enrolled	Canada: 61
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Turkey: 5
Worldwide total number of subjects	489
EEA total number of subjects	377

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)	20
Adults (18-64 years)	444
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were stratified at the time of randomization by the following factors: conditioning regimen (myeloablative or non-myeloablative); relatedness of donor (matched/related or mismatched/unrelated).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Voriconazole

Arm description:

Voriconazole loading dose regimen for first 24 hours and maintenance dose after first 24 hours.

Arm type	Experimental
Investigational medicinal product name	Voriconazole IV
Investigational medicinal product code	
Other name	VFEND
Pharmaceutical forms	Tablet, Powder for oral suspension
Routes of administration	Intravenous use

Dosage and administration details:

Voriconazole (tablet or powder for oral suspension) loading dose regimen intravenous (IV) for first 24 hours: 6 milligrams per kilogram (mg/kg) of body weight every 12 hours; maintenance dose (after first 24 hours) 4 mg/kg of body weight IV twice daily (BID).

Investigational medicinal product name	Voriconazole Oral
Investigational medicinal product code	
Other name	VFEND
Pharmaceutical forms	Powder for oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Voriconazole 200 mg tablet or powder for oral suspension by mouth (PO) BID (subjects greater than or equal to [≥] 40 kg body weight) or 100 mg tablet or powder for oral suspension twice daily (subjects less than [<] 40 kg body weight).

Arm title	Itraconazole

Arm description:

Itraconazole (Sporanox™ Liquid) loading dose on Days 0 and 1.

Arm type	Active comparator
Investigational medicinal product name	Itraconazole Oral
Investigational medicinal product code	
Other name	Sporanox
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Itraconazole (Sporanox™ Liquid) oral solution 200 mg PO BID.

Investigational medicinal product name	Itraconazole IV
Investigational medicinal product code	
Other name	Sporanox
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Itraconazole (Sporanox™ Liquid) 200 mg BID as loading dose on Days 0 and 1 then 200 mg once daily.

Number of subjects in period 1	Voriconazole	Itraconazole
Started	234	255
Completed	176	175
Not completed	58	80
'Failure of prophylaxis '	1	1
Consent withdrawn by subject	2	12
Adverse Event	15	13
Death	35	38
Unspecified	5	14
Lost to follow-up	-	1
'Fungal breakthrough infection '	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Voriconazole
Reporting group description:	
Voriconazole loading dose regimen for first 24 hours and maintenance dose after first 24 hours.	
Reporting group title	Itraconazole
Reporting group description:	
Itraconazole (Sporanox™ Liquid) loading dose on Days 0 and 1.	

Reporting group values	Voriconazole	Itraconazole	Total
Number of subjects	234	255	489
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	43.3	42.7	
standard deviation	± 14.4	± 14.6	-
Gender categorical Units: Subjects			
Female	96	100	196
Male	138	155	293

End points

End points reporting groups

Reporting group title	Voriconazole
Reporting group description:	
Voriconazole loading dose regimen for first 24 hours and maintenance dose after first 24 hours.	
Reporting group title	Itraconazole
Reporting group description:	
Itraconazole (Sporanox™ Liquid) loading dose on Days 0 and 1.	

Primary: Success at Day 180: Percent of Responders (Randomization Strata)

End point title	Success at Day 180: Percent of Responders (Randomization Strata)
End point description:	
Percent of responders (by randomization strata) with success of antifungal prophylaxis at 180 days after allogeneic HSCT. Success: alive at Day 180 (Visit 9), had not developed a breakthrough proven or probable IFI by Visit 9, and received full course of study drug prophylaxis without interruption of greater than 14 days in total during the prophylaxis period; defined as failure if these criteria were not met. Additionally, if subject withdrew from study completely before Visit 9, imputed as failure at Visit 9 (programmatically). Modified Intent to Treat (MITT): primary analysis population; all randomized subjects received at least 1 dose of randomized study drug and had allogeneic HSCT; data from 1 site excluded due to Good Clinical Practice (GCP) deviations, (n)=number of subjects with analyzable data at observation for voriconazole and itraconazole, respectively.	
End point type	Primary
End point timeframe:	
Day 180 (Visit 9)	

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: percent of subjects				
number (not applicable)				
Myeloablative/matched related (n=66, 85)	59.1	44.7		
Myeloablative/mismatched unrelated (n=59, 58)	52.5	25.9		
Non-myeloablative/matched related (n=58, 57)	34.5	28.1		
Non-myeloablative/mismatched unrelated (n=41, 41)	46.3	26.8		

Statistical analyses

Statistical analysis title	Success at Day 180: Percent of Responders
Statistical analysis description:	
Non-inferiority inferred if lower limit of 2-sided 95 percent (%) confidence interval (CI) for difference between treatment groups in proportion of subjects classified as "Success" at Day 180 after transplant is	

above -10%. If testing for non-inferiority was successful, then an assessment of superiority of voriconazole over itraconazole was carried out. Overall treatment difference adjusted randomization strata calculated using Fleiss method.

Comparison groups	Voriconazole v Itraconazole
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in adjusted responder rates
Point estimate	16.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	25.1

Notes:

[1] - Assuming a true success rate of 50% in voriconazole (Vori) treatment (Tx) group and 45% in itraconazole (Itra) Tx group, sample size of 232 subjects per group=90% power to demonstrate non-inferiority of Vori to Itra using pre-specified non-inferiority margin of -10%. Sample has at least 80% power to demonstrate superiority of Vori over Itra if true success rates for Vori and Itra are 57% and 44% respectively. Based on this, up to 500 subjects were to be enrolled to obtain 464 eligible subjects.

Secondary: Success at Day 100: Percent of Responders (Randomization Strata)

End point title	Success at Day 100: Percent of Responders (Randomization Strata)

End point description:

Percent of responders (by randomization strata) with success of antifungal prophylaxis at 100 days after allogeneic HSCT. Success defined as: alive at Day 100 (Visit 7), had not developed a breakthrough proven or probable IFI by Visit 7, and received full course of study drug prophylaxis without an interruption of >14 days in total during the prophylaxis period; defined as failure if these criteria were not met. Additionally, if subject withdrew from study completely before Visit 7, imputed as failure at Visit 7 (programmatically). MITT, data from 1 site excluded due to GCP deviations, (n)=number of subjects with analyzable data at observation for voriconazole and itraconazole, respectively.

End point type	Secondary

End point timeframe:

Day 100 (Visit 7)

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: percent of subjects				
number (not applicable)				
Myeloablative/matched related (n=66, 85)	65.2	50.6		
Myeloablative/mismatched unrelated (n=59, 58)	55.9	27.6		
Non-myeloablative/matched related (n=58, 57)	43.1	38.6		
Non-myeloablative/mismatched unrelated (n=41, 41)	48.8	36.6		

Statistical analyses

Statistical analysis title	Success at Day 100: Percent of Responders

Statistical analysis description:

Non-inferiority inferred if lower limit of 2-sided 95 percent (%) confidence interval (CI) for difference between treatment groups in proportion of subjects classified as "Success" at Day 100 after transplant is above -10%. If testing for non-inferiority was successful, then an assessment of superiority of voriconazole over itraconazole was carried out. Overall treatment difference adjusted randomization strata calculated using Fleiss method.

Comparison groups	Voriconazole v Itraconazole
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in adjusted responder rates
Point estimate	15.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	24.2

Secondary: Time to Breakthrough Invasive Fungal Infection (IFI)

End point title	Time to Breakthrough Invasive Fungal Infection (IFI)

End point description:

Summary of time (in days) from start of prophylaxis to first recorded occurrence of breakthrough proven or probable IFI. MITT, data from 1 site excluded due to GCP deviations. Analysis excludes additional data on IFIs that were only captured on European Organization for Research and Treatment of Cancer or Mycoses Study Group (EORTC or MSG) worksheets (not on Case Report Forms or in the database). Times were summarized only for subjects who experienced a breakthrough IFI.

End point type	Secondary

End point timeframe:

Day 1 up to Day 180 (Visit 9)

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: days				
arithmetic mean (confidence interval 95%)	119 (48 to 190)	77 (0 to 199.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Occurrence of Breakthrough IFI

End point title	Percent of Subjects With Occurrence of Breakthrough IFI

End point description:

Percent of subjects with occurrence of breakthrough IFI (proven or probable). Included all subjects in the MITT population. MITT, data from 1 site excluded due to GCP deviations. Analysis excludes additional data on IFIs that were only captured on EORTC or MSG worksheets (not on Case Report Forms or in the database).

End point type	Secondary

End point timeframe:

Day 1 up to Day 100 (Visit 7) and Day 180 (Visit 9)

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: percent of subjects				
number (not applicable)				
Day 100	0.9	1.2		
Day 180	1.3	1.7		

Statistical analyses

Statistical analysis title	Statistical Analysis for Day 100

Statistical analysis description:

Statistical analysis for percent of subjects with occurrence of breakthrough IFI for Day 100; difference in proportions (expressed as percentages) of voriconazole relative to itraconazole was analyzed. Difference in proportions (approximate result) was calculated.

Comparison groups	Voriconazole v Itraconazole
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7114 [2]
Method	difference in proportions
Parameter estimate	difference in proportions: percent
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	1.5

Notes:

[2] - The p-value was used to test the null hypothesis of no difference between the proportions.

Statistical analysis title	Statistical Analysis for Day 180

Statistical analysis description:

Statistical analysis for percent of subjects with occurrence of breakthrough IFI for Day 180; difference in proportions (expressed as percentages) of voriconazole relative to itraconazole was analyzed. Difference in proportions (approximate result) was calculated.

Comparison groups	Voriconazole v Itraconazole

Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7759 [3]
Method	difference in proportions
Parameter estimate	difference in proportions: percent
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	1.9

Notes:

[3] - The p-value was used to test the null hypothesis of no difference between the proportions.

Secondary: Survival: Percent of Subjects Who Died at or Before Day 180

End point title	Survival: Percent of Subjects Who Died at or Before Day 180

End point description:

Percent of subjects who died at or before Day 180, derived from the crude death rate. All subjects in the MITT population included in this proportion. MITT, data from 1 site excluded due to GCP deviations. Analysis does not include any deaths recorded in the long-term follow-up data (not available at time of analysis).

End point type	Secondary

End point timeframe:

Day 1 up to Day 180 (Visit 9)

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: percent of subjects				
number (not applicable)	17.85	18.25		

Statistical analyses

Statistical analysis title	Statistical Analysis on Day 180

Statistical analysis description:

Difference in proportions (expressed as a percentage) of voriconazole relative to itraconazole (approximate result) was calculated.

Comparison groups	Voriconazole v Itraconazole
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	other
Method	Logistic regression (logit model)
Parameter estimate	difference in proportions: percent
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	6.9

Secondary: Time to Discontinuation of Study Treatment

End point title	Time to Discontinuation of Study Treatment

End point description:

Time in days to discontinuation of study treatment defined as the number of days from first dose to last dose inclusive as recorded in the dosing log. MITT, data from 1 site excluded due to GCP deviations.

End point type	Secondary

End point timeframe:

Day 1 up to Day 180 (Visit 9)

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: days				
arithmetic mean (confidence interval 95%)	88.7 (80.6 to 96.8)	71.5 (64.9 to 78.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis on Day 180

Statistical analysis description:

Mann-Whitney test used to investigate the null hypothesis that the times to discontinuation of study medication in each treatment group come from the same distribution.

Comparison groups	Voriconazole v Itraconazole
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0026
Method	Non-parametric Mann-Whitney Test

Secondary: Survival: Percent of Subjects Who Died Within 1 Year

End point title	Survival: Percent of Subjects Who Died Within 1 Year

End point description:

Percent of subjects who died within 1 year after transplant, derived from the crude death rate. All subjects in the MITT population included in this proportion. Only deaths up until and including 365 days after first dose of study medication included in the analysis. MITT, data from 1 site excluded due to GCP deviations. Typically, subjects received first dose study treatment on the day of their transplant; however, some subjects started treatment up to 48 hours after transplant. Data summarized with first

day of study medication defined as Day 1.

End point type	Secondary

End point timeframe:

Day 1 up to 1 year (Day 365)

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: percent of subjects				
number (not applicable)	25.9	31.1		

Statistical analyses

Statistical analysis title	Statistical Analysis on Day 365

Statistical analysis description:

On Day 365, difference in proportions (expressed as a percentage), voriconazole relative to itraconazole (approximate result) was calculated.

Comparison groups	Voriconazole v Itraconazole
Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2487 [4]
Method	Logistic regression (logit model)
Parameter estimate	difference in proportions
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	3.4

Notes:

[4] - The p-value was used to test the null hypothesis of no difference between the proportions.

Secondary: Duration of Treatment

End point title	Duration of Treatment

End point description:

Median duration in days of treatment. Treatment is defined as the total number of days on which subjects took medication. MITT, data from 1 site excluded due to GCP deviations.

End point type	Secondary

End point timeframe:

Day 1 up to Day 180

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: days				
median (full range (min-max))	96 (1 to 258)	68 (3 to 223)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Use of Other Systemic Antifungal Agents as Empirical or Therapeutic Treatment

End point title	Percent of Subjects With Use of Other Systemic Antifungal Agents as Empirical or Therapeutic Treatment

End point description:

Percent of subjects who used other systemic antifungal agents as empirical or therapeutic treatment, defined as either empirical: subject took a systemic antifungal agent at any time after the day of first dose of medication and did not develop a breakthrough proven or probable IFI during the study or therapeutic: subject developed a breakthrough proven or probable IFI. MITT, data from 1 site excluded due to GCP deviations. Subjects who developed a breakthrough proven or probable IFI were identified only from the study database, not the EORTC or MSG worksheet. In addition, all agents identified to be antifungals were considered to be systemic.

End point type	Secondary

End point timeframe:

Day 1 up to Day 180

End point values	Voriconazole	Itraconazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224	241		
Units: percent of subjects				
number (not applicable)	40.6	49.4		

Statistical analyses

Statistical analysis title	Use of Other Systemic Antifungal Agents

Statistical analysis description:

Statistical Analysis for percent of subjects with use of other systemic antifungal agents as empirical or therapeutic treatment. Difference in proportions (expressed as a percentage), voriconazole relative to itraconazole.

Comparison groups	Voriconazole v Itraconazole

Number of subjects included in analysis	465
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.057 [5]
Method	Difference in proportions
Parameter estimate	Difference in proportions: percent
Point estimate	-8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	0.3

Notes:

[5] - The p-value was used to test the null hypothesis of no difference between the proportions.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline upto 7 days after last dose of investigational product

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Itraconazole

Reporting group description:

Itraconazole (Sporanox™ Liquid) oral solution 200 mg PO BID. Loading dose as IV formulation on Days 0 and 1.

Reporting group title	Voriconazole

Reporting group description:

Voriconazole (tablet or powder for oral suspension) loading dose regimen IV for first 24 hours: 6 mg/kg of body weight every 12 hours; maintenance dose (after first 24 hours) 4 mg/kg of body weight (IV) BID or 200 mg tablet or powder for oral suspension PO BID (subjects ≥40 kg body weight) or 100 mg tablet or powder for oral suspension twice daily (subjects < 40 kg body weight).

Serious adverse events	Itraconazole	Voriconazole	
Total subjects affected by serious adverse events			
subjects affected / exposed	95 / 255 (37.25%)	111 / 234 (47.44%)	
number of deaths (all causes)	47	40	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute leukaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myeloid leukaemia recurrent			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 255 (1.57%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Non-Hodgkin's lymphoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukaemia recurrent			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 255 (1.18%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Leukaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Disseminated large cell lymphoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Subdural haematoma evacuation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug intolerance			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 255 (1.18%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Disease progression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 255 (4.31%)	19 / 234 (8.12%)	
occurrences causally related to treatment / all	0 / 12	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease in intestine			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
alternative assessment type: Non-systematic			

subjects affected / exposed	8 / 255 (3.14%)	7 / 234 (2.99%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow transplant rejection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in liver			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic graft versus host disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 255 (1.18%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in liver			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	4 / 234 (1.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Graft versus host disease in gastrointestinal tract			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 255 (1.57%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute graft versus host disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 255 (2.75%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	1 / 7	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute lung injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 255 (1.18%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obliterative bronchiolitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 255 (1.96%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Psychiatric disorders			
Confusional state			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 255 (1.18%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus test			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gram stain positive			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serum ferritin increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus test positive			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	4 / 234 (1.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematocrit decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus test positive			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 255 (1.18%)	4 / 234 (1.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinsonism			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningorrhagia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Presyncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 255 (1.57%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic ischaemic neuropathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photopsia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal tenderness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 255 (2.35%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retching			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 255 (3.53%)	8 / 234 (3.42%)	
occurrences causally related to treatment / all	2 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysbacteriosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 255 (2.75%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	3 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Biliary colic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 255 (0.39%)	4 / 234 (1.71%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry skin			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 255 (2.35%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle twitching			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aspergillus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BK virus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (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			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus gastrointestinal infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human herpesvirus 6 infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 255 (4.31%)	9 / 234 (3.85%)	
occurrences causally related to treatment / all	0 / 11	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pseudomonal bacteraemia alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory syncytial virus infection alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bacteraemia alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 255 (1.18%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 255 (1.57%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pseudomonal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 255 (1.57%)	4 / 234 (1.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Septic shock			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 255 (1.57%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperferritinaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 255 (0.39%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 255 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Itraconazole	Voriconazole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	252 / 255 (98.82%)	228 / 234 (97.44%)	
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	49 / 255 (19.22%)	44 / 234 (18.80%)	
occurrences (all)	58	50	
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 255 (7.06%)	16 / 234 (6.84%)	
occurrences (all)	24	23	
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	31 / 255 (12.16%)	19 / 234 (8.12%)	
occurrences (all)	38	26	
Catheter site erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 255 (3.92%)	16 / 234 (6.84%)	
occurrences (all)	11	18	
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 255 (4.31%)	12 / 234 (5.13%)	
occurrences (all)	12	14	
Chills			
alternative assessment type: Non-systematic			
subjects affected / exposed	23 / 255 (9.02%)	17 / 234 (7.26%)	
occurrences (all)	25	22	
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	19 / 255 (7.45%)	35 / 234 (14.96%)	
occurrences (all)	23	41	
Oedema			
alternative assessment type: Non-systematic			

subjects affected / exposed	13 / 255 (5.10%)	12 / 234 (5.13%)	
occurrences (all)	15	13	
Oedema peripheral			
alternative assessment type: Non-systematic			
subjects affected / exposed	40 / 255 (15.69%)	35 / 234 (14.96%)	
occurrences (all)	53	48	
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	101 / 255 (39.61%)	105 / 234 (44.87%)	
occurrences (all)	134	146	
Mucosal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	142 / 255 (55.69%)	115 / 234 (49.15%)	
occurrences (all)	165	129	
Immune system disorders			
Acute graft versus host disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 255 (6.27%)	15 / 234 (6.41%)	
occurrences (all)	16	16	
Graft versus host disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 255 (10.59%)	26 / 234 (11.11%)	
occurrences (all)	30	30	
Graft versus host disease in skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 255 (7.06%)	12 / 234 (5.13%)	
occurrences (all)	20	16	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 255 (11.76%)	20 / 234 (8.55%)	
occurrences (all)	37	28	
Dyspnoea			
alternative assessment type: Non-systematic			

subjects affected / exposed	14 / 255 (5.49%)	17 / 234 (7.26%)	
occurrences (all)	14	18	
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	42 / 255 (16.47%)	45 / 234 (19.23%)	
occurrences (all)	52	55	
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 255 (8.63%)	20 / 234 (8.55%)	
occurrences (all)	24	22	
Rhinorrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	16 / 255 (6.27%)	16 / 234 (6.84%)	
occurrences (all)	18	16	
Psychiatric disorders			
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 255 (6.67%)	22 / 234 (9.40%)	
occurrences (all)	17	24	
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 255 (7.06%)	15 / 234 (6.41%)	
occurrences (all)	19	18	
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 255 (1.57%)	12 / 234 (5.13%)	
occurrences (all)	4	15	
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 255 (3.14%)	13 / 234 (5.56%)	
occurrences (all)	10	41	
Liver function test abnormal			
alternative assessment type: Non-systematic			

subjects affected / exposed	10 / 255 (3.92%)	18 / 234 (7.69%)	
occurrences (all)	12	18	
Weight increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 255 (5.10%)	10 / 234 (4.27%)	
occurrences (all)	13	10	
Cardiac disorders			
Tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 255 (2.35%)	13 / 234 (5.56%)	
occurrences (all)	8	13	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	69 / 255 (27.06%)	63 / 234 (26.92%)	
occurrences (all)	83	84	
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 255 (3.92%)	13 / 234 (5.56%)	
occurrences (all)	12	15	
Paraesthesia			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 255 (1.96%)	14 / 234 (5.98%)	
occurrences (all)	5	18	
Tremor			
alternative assessment type: Non-systematic			
subjects affected / exposed	19 / 255 (7.45%)	10 / 234 (4.27%)	
occurrences (all)	27	10	
Blood and lymphatic system disorders			
Neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 255 (11.76%)	21 / 234 (8.97%)	
occurrences (all)	30	23	
Febrile neutropenia			
alternative assessment type: Non-systematic			

subjects affected / exposed	68 / 255 (26.67%)	51 / 234 (21.79%)	
occurrences (all)	76	57	
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 255 (11.76%)	30 / 234 (12.82%)	
occurrences (all)	40	32	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	41 / 255 (16.08%)	35 / 234 (14.96%)	
occurrences (all)	54	51	
Eye disorders			
Visual impairment			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 255 (0.78%)	15 / 234 (6.41%)	
occurrences (all)	3	16	
Gastrointestinal disorders			
Dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 255 (8.63%)	25 / 234 (10.68%)	
occurrences (all)	30	33	
Haemorrhoids			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 255 (3.92%)	12 / 234 (5.13%)	
occurrences (all)	10	12	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	91 / 255 (35.69%)	86 / 234 (36.75%)	
occurrences (all)	128	129	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	132 / 255 (51.76%)	97 / 234 (41.45%)	
occurrences (all)	188	135	
Constipation			
alternative assessment type: Non-systematic			

subjects affected / exposed	21 / 255 (8.24%)	41 / 234 (17.52%)	
occurrences (all)	22	45	
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	21 / 255 (8.24%)	23 / 234 (9.83%)	
occurrences (all)	23	27	
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	51 / 255 (20.00%)	45 / 234 (19.23%)	
occurrences (all)	61	56	
Oral pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 255 (4.71%)	15 / 234 (6.41%)	
occurrences (all)	15	15	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	104 / 255 (40.78%)	78 / 234 (33.33%)	
occurrences (all)	148	107	
Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 255 (5.88%)	12 / 234 (5.13%)	
occurrences (all)	15	15	
Hepatobiliary disorders			
Hepatocellular injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 255 (3.14%)	12 / 234 (5.13%)	
occurrences (all)	11	13	
Cholestasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 255 (3.92%)	14 / 234 (5.98%)	
occurrences (all)	10	15	
Hepatotoxicity			
alternative assessment type: Non-systematic			

subjects affected / exposed	8 / 255 (3.14%)	19 / 234 (8.12%)	
occurrences (all)	8	23	
Hyperbilirubinaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 255 (5.10%)	5 / 234 (2.14%)	
occurrences (all)	14	5	
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	45 / 255 (17.65%)	48 / 234 (20.51%)	
occurrences (all)	67	79	
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 255 (9.41%)	25 / 234 (10.68%)	
occurrences (all)	29	29	
Erythema			
alternative assessment type: Non-systematic			
subjects affected / exposed	39 / 255 (15.29%)	43 / 234 (18.38%)	
occurrences (all)	51	63	
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 255 (4.71%)	16 / 234 (6.84%)	
occurrences (all)	12	18	
Petechiae			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 255 (5.10%)	7 / 234 (2.99%)	
occurrences (all)	14	8	
Renal and urinary disorders			
Renal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 255 (4.71%)	19 / 234 (8.12%)	
occurrences (all)	16	19	
Dysuria			
alternative assessment type: Non-systematic			

subjects affected / exposed	15 / 255 (5.88%)	13 / 234 (5.56%)	
occurrences (all)	19	15	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
alternative assessment type: Non-systematic			
subjects affected / exposed	24 / 255 (9.41%)	21 / 234 (8.97%)	
occurrences (all)	29	26	
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 255 (10.59%)	33 / 234 (14.10%)	
occurrences (all)	31	38	
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 255 (8.63%)	18 / 234 (7.69%)	
occurrences (all)	24	24	
Infections and infestations			
Cytomegalovirus infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 255 (6.67%)	22 / 234 (9.40%)	
occurrences (all)	19	25	
Device related infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 255 (3.53%)	12 / 234 (5.13%)	
occurrences (all)	12	12	
Folliculitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 255 (4.31%)	12 / 234 (5.13%)	
occurrences (all)	11	12	
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 255 (3.14%)	12 / 234 (5.13%)	
occurrences (all)	8	13	
Metabolism and nutrition disorders			

Hyperglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 255 (3.53%)	12 / 234 (5.13%)	
occurrences (all)	9	14	
Fluid retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 255 (5.88%)	10 / 234 (4.27%)	
occurrences (all)	17	12	
Fluid overload			
alternative assessment type: Non-systematic			
subjects affected / exposed	20 / 255 (7.84%)	8 / 234 (3.42%)	
occurrences (all)	22	9	
Diabetes mellitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 255 (4.71%)	13 / 234 (5.56%)	
occurrences (all)	13	13	
Decreased appetite			
alternative assessment type: Non-systematic			
subjects affected / exposed	41 / 255 (16.08%)	27 / 234 (11.54%)	
occurrences (all)	47	31	
Hypokalaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 255 (11.76%)	12 / 234 (5.13%)	
occurrences (all)	39	13	
Hypomagnesaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 255 (11.76%)	21 / 234 (8.97%)	
occurrences (all)	36	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2006	Approved SAE waiver for bone marrow suppression was added. The safety language in the protocol was revised to address new requirements related to Exposure In Utero.
06 December 2007	The reasons for this global amendment were to add the concomitant use of St. John's Wort as an exclusion criterion to the study, in order to keep the protocol inline with the newly updated summary of product characteristics of voriconazole and to clarify the recording requirements of serious and non-serious adverse events on the case report form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Data was excluded from 1 site due to Good Clinical Practices deviations.

Notes: