Clinical trial results:
A Phase III randomised, double-blind, controlled, parallel group study of intravenous volasertib in combination with subcutaneous low-dose cytarabine vs. placebo + low-dose cytarabine in patients 65 years with previously untreated acute myeloid leukaemia, who are ineligible for intensive remission induction therapy

Summary

EudraCT number	2012-002487-27
Trial protocol	BE DE PT GR AT FI ES IT CZ NL HU PL FR
Global end of trial date	28 May 2021

Results information

Result version number	v2 (current)
This version publication date	02 December 2021
First version publication date	01 October 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1230.14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01721876
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 +18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 +18002430127, clintriage.rdg@boehringer-ingelheim.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	21 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2014
Global end of trial reached?	Yes
Global end of trial date	28 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy, safety, and pharmacokinetics of intravenous volasertib + subcutaneous low-dose cytarabine (LDAC) in patients ≥65 years of age with previously untreated acute myeloid leukaemia (AML), who are ineligible for intensive remission induction therapy

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 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	Argentina: 2
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 63
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Czechia: 17
Country: Number of subjects enrolled	Finland: 17
Country: Number of subjects enrolled	France: 74
Country: Number of subjects enrolled	Germany: 168
Country: Number of subjects enrolled	Greece: 49
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Korea, Republic of: 57
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 19

Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	769
EEA total number of subjects	578

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	769
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients aged 65 years or more with previously untreated acute myeloid leukaemia, who are ineligible for intensive remission induction therapy were recruited in the phase III randomised, double-blind, placebo-controlled, parallel group study.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended a specialist sites which ensured that they (the patients) met all strictly implemented inclusion/exclusion criteria. Patients were not to be randomized to trial treatment if any one of the specific entry criteria was violated.

Period 1

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

Blinding implementation details:

It was a randomised, placebo-controlled, double-blind parallel group study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Low-dose Cytarabine

Arm description:

Patients received placebo matching to Volasertib 350 milligram (mg) intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Arm type	Placebo
Investigational medicinal product name	Low-dose Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received placebo matching to Volasertib 350 milligram (mg) intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received placebo matching to Volasertib 350 milligram (mg) intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Arm title	Volasertib + Low-dose Cytarabine

Arm description:

Patients received Volasertib 350 mg intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, wherein no dose increase was allowed after a dose reduction, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Arm type	Experimental

Investigational medicinal product name	Low-dose Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received Volasertib 350 mg intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, wherein no dose increase was allowed after a dose reduction, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle, wherein no dose reduction or increase was allowed according to protocol; however, individual administrations could be skipped at the investigator's discretion.

Investigational medicinal product name	Volasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received Volasertib 350 mg intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, wherein no dose increase was allowed after a dose reduction, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle, wherein no dose reduction or increase was allowed according to protocol; however, individual administrations could be skipped at the investigator's discretion.

Number of subjects in period 1[1]	Placebo + Low-dose Cytarabine	Volasertib + Low-dose Cytarabine
Started	222	444
Treated	221	440
Completed	0	0
Not completed	222	444
Protocol deviation	2	1
Disease progression / relapse	123	156
Adverse event, serious fatal	6	13
Adverse event, non-fatal	41	165
Consent withdrawn by subject	15	38
Sponsor terminated trial	-	4
Reason not listed	34	63
Not treated	1	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 769 enrolled subjects, 677 subjects were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Low-dose Cytarabine
Reporting group description:	
Patients received placebo matching to Volasertib 350 milligram (mg) intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.	
Reporting group title	Volasertib + Low-dose Cytarabine
Reporting group description:	
Patients received Volasertib 350 mg intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, wherein no dose increase was allowed after a dose reduction, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.	

Reporting group values	Placebo + Low-dose Cytarabine	Volasertib + Low-dose Cytarabine	Total
Number of subjects	222	444	666
Age categorical			
The randomised set (RS) included all patients who had been randomised at the database snapshot.			
Units: Subjects			
Age Continuous			
RS			
Units: years			
arithmetic mean	75.5	75.2	
standard deviation	± 4.9	± 5.4	-
Sex: Female, Male			
RS			
Units: Subjects			
Female	87	203	290
Male	135	241	376
Race (NIH/OMB)			
RS			
Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	39	74	113
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	2
White	158	328	486
More than one race	0	0	0
Unknown or Not Reported	25	38	63
Ethnicity (NIH/OMB)			
RS			
Units: Subjects			
Hispanic or Latino	10	16	26
Not Hispanic or Latino	194	399	593
Unknown or Not Reported	18	29	47

End points

End points reporting groups

Reporting group title	Placebo + Low-dose Cytarabine

Reporting group description:

Patients received placebo matching to Volasertib 350 milligram (mg) intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Reporting group title	Volasertib + Low-dose Cytarabine

Reporting group description:

Patients received Volasertib 350 mg intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, wherein no dose increase was allowed after a dose reduction, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Primary: Objective Response (OR)

End point title	Objective Response (OR)

End point description:

OR is the number of patients who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi), where OR was based on the best response attained during the treatment period. Objective response (CR + CRi) was also analysed by the stratification factors eastern cooperative oncology group (ECOG) performance score (PS) and type of acute myeloid leukaemia (AML). The randomised set (RS) included all patients who had been randomised at the database snapshot.

End point type	Primary

End point timeframe:

Response assessment was performed at the end of every 2nd cycle, (i.e. at the end of Cycle 2, 4, 6, 8, etc., and at end of treatment), i.e. up to 52 months.

End point values	Placebo + Low-dose Cytarabine	Volasertib + Low-dose Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[1]	444[2]		
Units: Participants	38	123		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

This analysis was exploratory and descriptive.

Comparison groups	Placebo + Low-dose Cytarabine v Volasertib + Low-dose Cytarabine
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0024 [4]
Method	Cochran-Mantel-Haenszel

Parameter estimate	Odds ratio (OR)
Point estimate	1.8751
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2432
upper limit	2.8281

Notes:

[3] - The 2-sided test of the hypothesis was performed at a 0.05 level of significance. An odds ratio (OR) = 1 would indicate that the odds of achieving CR+CRi with Volasertib + Low-dose Cytarabine is equal to the odds of achieving CR+CRi with Placebo + Low-dose Cytarabine , whereas an OR ≠ 1 would indicate the opposite. H0, CR+CRi: OR = 1 vs. Ha, CR+CRi: OR ≠ 1.

[4] - The common odds ratio is calculated by Mantel−Haenszel estimate adjusting for the two stratification factors (baseline ECOG and type of AML). If odds ratio is above 1 then it favours Volasertib+Low-dose Cytarabine.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is the key secondary endpoint and was measured from the date of randomization until death from any cause. Patients who were lost to follow-up were censored on the last date they were known to be alive. The final analysis of OS was performed after at least 574 OS events had accrued.

End point type	Secondary

End point timeframe:

From randomization until death due to any cause, up to 1557 days.

End point values	Placebo + Low-dose Cytarabine	Volasertib + Low-dose Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[5]	444[6]		
Units: Months				
median (confidence interval 95%)	6.5 (4.9 to 8.0)	5.6 (4.5 to 6.8)		

Notes:

[5] - RS

[6] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is calculated from Cox proportional hazard model stratified by baseline ECOG and type of AML. If hazard ratio is below 1 then it favours volasertib. This analysis was exploratory and descriptive.

Comparison groups	Placebo + Low-dose Cytarabine v Volasertib + Low-dose Cytarabine
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.7571 [8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	

level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.2

Notes:

[7] - The hazard ratio (HR) between Volasertib + Low-dose Cytarabine and Placebo + Low-dose Cytarabine was tested against 1. The null hypothesis, H0,OS, was that the hazards are equal between Volasertib + Low-dose Cytarabine and Placebo + Low-dose Cytarabine, whereas the alternative hypothesis, Ha,OS, was that the hazards are not equal between the 2 treatment arms. H0, OS: HR = 1 vs. Ha, OS: HR ≠ 1.

[8] - P−value is calculated from log−rank test stratified by baseline ECOG (0−1 vs. 2) and type of AML (denovo vs. secondary).

Secondary: Event-free survival (EFS)

End point title	Event-free survival (EFS)

End point description:

EFS was measured from the date of randomisation to the date of progression or relapse, or death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

From randomization until disease progression or relapse or death from any cause, up to 1557 days.

End point values	Placebo + Low-dose Cytarabine	Volasertib + Low-dose Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222[9]	444[10]		
Units: Months				
median (confidence interval 95%)	2.8 (2.1 to 4.9)	3.3 (2.6 to 4.2)		

Notes:

[9] - RS

[10] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio is calculated from Cox proportional hazard model stratified by baseline ECOG and type of AML. If hazard ratio is below 1 then it favours volasertib. This analysis was exploratory and descriptive.

Comparison groups	Placebo + Low-dose Cytarabine v Volasertib + Low-dose Cytarabine
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6718 [11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.2

Notes:

[11] - P−value is calculated from log−rank test stratified by baseline ECOG (0−1 vs. 2) and type of AML (denovo vs. secondary).

Secondary: Relapse-free survival (RFS)

End point title	Relapse-free survival (RFS)

End point description:

RFS was defined only for patients who achieved CR or CRi; it was measured from the date of achievement of a remission until the date of relapse or death from any cause. Patients not known to have relapsed or died at last follow-up were censored on the date they were last examined.

Analysis Population Description: all patients in the RS who achieved best overall response of CR or CRi.

End point type	Secondary

End point timeframe:

From randomization until disease progression or relapse or death from any cause, up to 1557 days.

End point values	Placebo + Low-dose Cytarabine	Volasertib + Low-dose Cytarabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38[12]	123[13]		
Units: Months				
median (confidence interval 95%)				
RFS in months	18.7 (11.3 to 99999)	13.1 (6.2 to 99999)		

Notes:

[12] - 99999 = cannot be estimated due to insufficient number of participants with events.

[13] - 99999 = cannot be estimated due to insufficient number of participants with events.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Low-dose Cytarabine v Volasertib + Low-dose Cytarabine
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other[14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.7

Notes:

[14] - Hazard ratio is calculated from Cox proportional hazard model stratified by baseline ECOG and type of AML. If hazard ratio is below 1 then it favours volasertib.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 21 days after last drug administration, i.e., up to 48 months.

Adverse event reporting additional description:

The treated set included all patients who were dispensed study medication and were documented to have taken at least one dose of Volasertib, placebo, or Low-dose Cytarabine. One patient was randomised to the Volasertib + Low-dose Cytarabine arm but only took Low-dose Cytarabine and was therefore allocated to the Placebo + Low-dose Cytarabine arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Subjects assigned to Volasertib + Low-dose Cytarabine

Reporting group description:

Patients received Volasertib 350 mg intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, wherein no dose increase was allowed after a dose reduction, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Reporting group title	Subjects assigned to Placebo + Low-dose Cytarabine

Reporting group description:

Patients received placebo matching to Volasertib 350 milligram (mg) intravenous infusion for 1 hour on day 1 and day 15 of each 28-day cycle, in combination with Cytarabine 20 mg subcutaneous injection given twice daily at 12 hours interval from day 1 to 10 of each 28-day cycle.

Serious adverse events	Subjects assigned to Volasertib + Low-dose Cytarabine	Subjects assigned to Placebo + Low-dose Cytarabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	380 / 439 (86.56%)	163 / 222 (73.42%)	
number of deaths (all causes)	373	201	
number of deaths resulting from adverse events	39	13	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 439 (1.14%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Angioplasty			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to	0 / 0	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of thorax			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	22 / 439 (5.01%)	17 / 222 (7.66%)	
occurrences causally related to treatment / all	0 / 22	0 / 17	
deaths causally related to treatment / all	0 / 13	0 / 12	
Neoplasm skin			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (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	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloproliferative neoplasm			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Allergy to vaccine			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 439 (1.37%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	2 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site phlebitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Chest pain			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to	0 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 439 (0.46%)	5 / 222 (2.25%)	
occurrences causally related to treatment / all	2 / 2	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	15 / 439 (3.42%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	3 / 16	0 / 3	
deaths causally related to treatment / all	1 / 2	0 / 0	
Induration			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	5 / 439 (1.14%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	33 / 439 (7.52%)	19 / 222 (8.56%)	
occurrences causally related to treatment / all	11 / 38	6 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 439 (0.91%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (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			
Allergic transfusion reaction			

subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 439 (0.00%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	4 / 439 (0.91%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Tracheal obstruction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Transfusion reaction			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related acute lung injury			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related circulatory overload			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (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			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure orthostatic decreased			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 439 (0.46%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	

deaths causally related to treatment / all	0 / 0	0 / 0	
Haematocrit decreased			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 439 (0.91%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	

deaths causally related to treatment / all	0 / 2	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 439 (1.37%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	3 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	10 / 439 (2.28%)	8 / 222 (3.60%)	
occurrences causally related to treatment / all	2 / 11	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	4 / 439 (0.91%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	

Cardiac disorder			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Left ventricular dysfunction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (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 / 439 (0.23%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	

occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	3 / 439 (0.68%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 2	
Bronchospasm			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 439 (0.68%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	6 / 439 (1.37%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	

deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	4 / 439 (0.91%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	11 / 439 (2.51%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	0 / 11	2 / 6	
deaths causally related to treatment / all	0 / 2	1 / 3	
Respiratory tract haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 439 (4.56%)	10 / 222 (4.50%)	
occurrences causally related to treatment / all	18 / 23	7 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	3 / 439 (0.68%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	5 / 439 (1.14%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Febrile neutropenia			
subjects affected / exposed	203 / 439 (46.24%)	42 / 222 (18.92%)	
occurrences causally related to treatment / all	164 / 304	35 / 66	
deaths causally related to treatment / all	2 / 6	1 / 1	
Haemolytic anaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic disorder			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic diathesis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Leukocytosis			
subjects affected / exposed	0 / 439 (0.00%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypofibrinogenaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	13 / 439 (2.96%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	9 / 14	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	23 / 439 (5.24%)	9 / 222 (4.05%)	
occurrences causally related to treatment / all	21 / 28	7 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Brain stem haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	3 / 439 (0.68%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	3 / 439 (0.68%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to	0 / 3	0 / 1	

treatment / all		
deaths causally related to treatment / all	0 / 0	0 / 0
Dizziness		
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Embolic cerebral infarction		
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhage intracranial		
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)
occurrences causally related to treatment / all	1 / 1	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0
Haemorrhagic stroke		
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Hypotonia		
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Seizure		
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiparesis		
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Sneddon's syndrome		
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stupor			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 439 (0.68%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness transient			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 439 (1.82%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	2 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	4 / 439 (0.91%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 439 (0.91%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric panniculitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	5 / 439 (1.14%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (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 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	6 / 439 (1.37%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	5 / 6	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	19 / 439 (4.33%)	7 / 222 (3.15%)	
occurrences causally related to treatment / all	3 / 22	1 / 7	
deaths causally related to treatment / all	1 / 1	0 / 1	
Haematuria			
subjects affected / exposed	4 / 439 (0.91%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	6 / 439 (1.37%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			

subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema nodosum			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin haemorrhage			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to	0 / 0	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to	1 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 439 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatininaemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	2 / 439 (0.46%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	3 / 439 (0.68%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacillus infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	5 / 439 (1.14%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	4 / 439 (0.91%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 439 (0.68%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Bronchopulmonary aspergillosis			
subjects affected / exposed	12 / 439 (2.73%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	4 / 12	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Campylobacter sepsis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 439 (0.68%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			

subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 439 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	5 / 439 (1.14%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 439 (0.23%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	4 / 439 (0.91%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fungal skin infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 439 (0.68%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Laryngitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis bacterial			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	7 / 439 (1.59%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	6 / 8	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocarditis septic			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis fungal			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perichondritis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	113 / 439 (25.74%)	44 / 222 (19.82%)	
occurrences causally related to treatment / all	51 / 127	13 / 49	

deaths causally related to treatment / all	10 / 28	4 / 6	
Pneumonia klebsiella			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	7 / 439 (1.59%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 8	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pseudomembranous colitis			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	4 / 439 (0.91%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary sepsis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pseudomonas infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary tuberculosis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (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			
subjects affected / exposed	7 / 439 (1.59%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 7	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection fungal			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	44 / 439 (10.02%)	9 / 222 (4.05%)	
occurrences causally related to treatment / all	12 / 46	3 / 10	
deaths causally related to treatment / all	3 / 17	1 / 3	
Septic shock			
subjects affected / exposed	28 / 439 (6.38%)	10 / 222 (4.50%)	
occurrences causally related to treatment / all	9 / 31	7 / 10	
deaths causally related to treatment / all	5 / 14	1 / 2	
Sinusitis aspergillus			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 439 (0.23%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	4 / 439 (0.91%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	3 / 439 (0.68%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 439 (0.46%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas sepsis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular abscess			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 439 (0.23%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis bacterial			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	2 / 439 (0.46%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 439 (1.14%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	12 / 439 (2.73%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	3 / 12	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium bacteraemia			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 439 (0.23%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 439 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Subjects assigned to Volasertib + Low-dose Cytarabine	Subjects assigned to Placebo + Low-dose Cytarabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	404 / 439 (92.03%)	203 / 222 (91.44%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 439 (7.06%)	7 / 222 (3.15%)	
occurrences (all)	36	7	
Haematoma			
subjects affected / exposed	55 / 439 (12.53%)	20 / 222 (9.01%)	
occurrences (all)	64	25	
Hypotension			
subjects affected / exposed	23 / 439 (5.24%)	9 / 222 (4.05%)	
occurrences (all)	28	10	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	22 / 439 (5.01%)	8 / 222 (3.60%)	
occurrences (all)	29	8	
Chills			
subjects affected / exposed	26 / 439 (5.92%)	12 / 222 (5.41%)	
occurrences (all)	39	15	
Asthenia			

subjects affected / exposed	64 / 439 (14.58%)	42 / 222 (18.92%)	
occurrences (all)	118	53	
Oedema			
subjects affected / exposed	36 / 439 (8.20%)	13 / 222 (5.86%)	
occurrences (all)	43	15	
Mucosal inflammation			
subjects affected / exposed	63 / 439 (14.35%)	11 / 222 (4.95%)	
occurrences (all)	95	15	
Fatigue			
subjects affected / exposed	62 / 439 (14.12%)	29 / 222 (13.06%)	
occurrences (all)	95	43	
Oedema peripheral			
subjects affected / exposed	75 / 439 (17.08%)	42 / 222 (18.92%)	
occurrences (all)	90	59	
Pain			
subjects affected / exposed	31 / 439 (7.06%)	10 / 222 (4.50%)	
occurrences (all)	34	10	
Pyrexia			
subjects affected / exposed	85 / 439 (19.36%)	58 / 222 (26.13%)	
occurrences (all)	132	79	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	38 / 439 (8.66%)	21 / 222 (9.46%)	
occurrences (all)	51	21	
Confusional state			
subjects affected / exposed	22 / 439 (5.01%)	7 / 222 (3.15%)	
occurrences (all)	24	7	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	26 / 439 (5.92%)	9 / 222 (4.05%)	
occurrences (all)	27	9	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 439 (5.92%)	16 / 222 (7.21%)	
occurrences (all)	31	29	
Weight decreased			

subjects affected / exposed	39 / 439 (8.88%)	20 / 222 (9.01%)	
occurrences (all)	44	21	
Electrocardiogram QT prolonged			
subjects affected / exposed	32 / 439 (7.29%)	8 / 222 (3.60%)	
occurrences (all)	53	9	
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 439 (4.33%)	14 / 222 (6.31%)	
occurrences (all)	21	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	137 / 439 (31.21%)	53 / 222 (23.87%)	
occurrences (all)	361	120	
Febrile neutropenia			
subjects affected / exposed	101 / 439 (23.01%)	28 / 222 (12.61%)	
occurrences (all)	142	50	
Leukopenia			
subjects affected / exposed	45 / 439 (10.25%)	23 / 222 (10.36%)	
occurrences (all)	114	38	
Neutropenia			
subjects affected / exposed	124 / 439 (28.25%)	34 / 222 (15.32%)	
occurrences (all)	449	93	
Thrombocytopenia			
subjects affected / exposed	163 / 439 (37.13%)	59 / 222 (26.58%)	
occurrences (all)	605	195	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	71 / 439 (16.17%)	28 / 222 (12.61%)	
occurrences (all)	99	33	
Cough			
subjects affected / exposed	95 / 439 (21.64%)	21 / 222 (9.46%)	
occurrences (all)	121	25	
Dyspnoea			
subjects affected / exposed	76 / 439 (17.31%)	30 / 222 (13.51%)	
occurrences (all)	90	35	
Oropharyngeal pain			

subjects affected / exposed	28 / 439 (6.38%)	4 / 222 (1.80%)	
occurrences (all)	33	4	
Pleural effusion			
subjects affected / exposed	17 / 439 (3.87%)	17 / 222 (7.66%)	
occurrences (all)	18	20	
Nervous system disorders			
Dizziness			
subjects affected / exposed	43 / 439 (9.79%)	18 / 222 (8.11%)	
occurrences (all)	58	22	
Headache			
subjects affected / exposed	48 / 439 (10.93%)	23 / 222 (10.36%)	
occurrences (all)	74	32	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	47 / 439 (10.71%)	26 / 222 (11.71%)	
occurrences (all)	57	36	
Abdominal pain upper			
subjects affected / exposed	30 / 439 (6.83%)	14 / 222 (6.31%)	
occurrences (all)	34	18	
Stomatitis			
subjects affected / exposed	75 / 439 (17.08%)	13 / 222 (5.86%)	
occurrences (all)	94	15	
Nausea			
subjects affected / exposed	123 / 439 (28.02%)	79 / 222 (35.59%)	
occurrences (all)	183	116	
Diarrhoea			
subjects affected / exposed	116 / 439 (26.42%)	49 / 222 (22.07%)	
occurrences (all)	176	73	
Constipation			
subjects affected / exposed	122 / 439 (27.79%)	55 / 222 (24.77%)	
occurrences (all)	156	71	
Vomiting			
subjects affected / exposed	71 / 439 (16.17%)	27 / 222 (12.16%)	
occurrences (all)	97	36	
Dyspepsia			
subjects affected / exposed	22 / 439 (5.01%)	9 / 222 (4.05%)	

occurrences (all)	26	13	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	30 / 439 (6.83%)	4 / 222 (1.80%)	
occurrences (all)	32	4	
Petechiae			
subjects affected / exposed	73 / 439 (16.63%)	24 / 222 (10.81%)	
occurrences (all)	93	29	
Pruritus			
subjects affected / exposed	27 / 439 (6.15%)	17 / 222 (7.66%)	
occurrences (all)	45	22	
Rash			
subjects affected / exposed	72 / 439 (16.40%)	30 / 222 (13.51%)	
occurrences (all)	96	33	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	45 / 439 (10.25%)	30 / 222 (13.51%)	
occurrences (all)	58	32	
Pain in extremity			
subjects affected / exposed	30 / 439 (6.83%)	12 / 222 (5.41%)	
occurrences (all)	37	17	
Back pain			
subjects affected / exposed	50 / 439 (11.39%)	18 / 222 (8.11%)	
occurrences (all)	59	24	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	82 / 439 (18.68%)	43 / 222 (19.37%)	
occurrences (all)	115	62	
Hyperuricaemia			
subjects affected / exposed	13 / 439 (2.96%)	13 / 222 (5.86%)	
occurrences (all)	14	24	
Hypomagnesaemia			
subjects affected / exposed	23 / 439 (5.24%)	13 / 222 (5.86%)	
occurrences (all)	27	14	
Hypoalbuminaemia			

subjects affected / exposed	24 / 439 (5.47%)	14 / 222 (6.31%)	
occurrences (all)	30	29	
Hypokalaemia			
subjects affected / exposed	120 / 439 (27.33%)	37 / 222 (16.67%)	
occurrences (all)	166	48	
Hypophosphataemia			
subjects affected / exposed	22 / 439 (5.01%)	6 / 222 (2.70%)	
occurrences (all)	30	10	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	25 / 439 (5.69%)	5 / 222 (2.25%)	
occurrences (all)	28	5	
Oral herpes			
subjects affected / exposed	31 / 439 (7.06%)	10 / 222 (4.50%)	
occurrences (all)	45	10	
Urinary tract infection			
subjects affected / exposed	24 / 439 (5.47%)	4 / 222 (1.80%)	
occurrences (all)	30	4	
Pneumonia			
subjects affected / exposed	38 / 439 (8.66%)	9 / 222 (4.05%)	
occurrences (all)	43	9	
Nasopharyngitis			
subjects affected / exposed	18 / 439 (4.10%)	13 / 222 (5.86%)	
occurrences (all)	24	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2013	Amendment 1 was submitted because the volasertib vial size was to change with the next resupply to the sites. The amendment also included minor corrections and clarifications.
25 June 2013	Amendment 2 was issued to incorporate several minor corrections and clarifications in the clinical trial protocol (CTP).
26 September 2014	Amendment 3 was issued to specify that the database snapshot for the interim analysis was targeted as close as possible to the projected date of recruitment completion and was not to interfere with the completion of recruitment.
28 November 2014	Amendment 4 was issued and implemented without IRB/IEC/Competent Authority approval, as the changes involved administrative or logistical aspects only. The definition of CR and CRi were further refined. For CR, independence of red blood cell transfusions was defined as no transfusion for at least 7 days prior to response assessment, and it was specified that there is no minimum duration of response required. For CRi, it was clarified that incomplete blood count recovery includes red blood cells (with potential need for red blood cell transfusions).
29 January 2015	Amendment 5 which was issued and implemented immediately and communicated to all relevant investigators, competent authorities and ethics committees in a timely manner to eliminate hazard: 1. Inform investigators of the key results of the primary analysis 2. Unblind all patients currently on treatment 3. Allow patients to continue study treatment at the discretion of the investigators
24 May 2017	Amendment 6 was issued on 24 May 2017 after approval of the Institutional Review Board/Independent Ethics Committee/Competent Authority. After the final analysis (based on at least 574 Overal Survival) was conducted as planned, patients still on treatment and with clinical benefit from Volasertib and/or Low-dose Cytarabine were kept on treatment in this trial. The mandatory protocol procedures as well as data collection were reduced after the planned final analysis was conducted.

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.

The final analysis presented in this report was conducted after 574 OS events had occurred. The final analysis was exploratory and descriptive.

Notes: