Clinical trial results:
A Phase 2 Open-label, AC220 Monotherapy Efficacy (ACE) Study in Patients with Acute Myeloid Leukemia (AML) with and without FLT3-ITD Activating Mutations

Summary

EudraCT number	2009-013093-41
Trial protocol	FR DE ES NL PL IT GB
Global end of trial date	31 December 2014

Results information

Result version number	v1 (current)
This version publication date	23 December 2018
First version publication date	23 December 2018

Trial information

Trial identification

Sponsor protocol code	AC220-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00989261
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Global Clinical Leader, Daiichi Sankyo, Inc., 1 9089926400,
Scientific contact	Global Clinical Leader, Daiichi Sankyo, Inc., 1 9089926400,

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	28 September 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 September 2012
Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determination of:
•Overall complete remission rate, defined as the confirmed rate of complete remission (CR) plus complete remission with incomplete platelet (CRp) or incomplete hematological recovery (CRi) (ie, CR + CRp + CRi)
•Complete remission rate, defined as the confirmed rate of CR

The basic results in the Clinical Study Report reflected here, focus on the combined data across both the Exploratory and Confirmatory Stages, as the results were able to be integrated and, in doing so, provide a more robust perspective on the objectives. All combination data tables were reprogrammed based on the original data and the results were validated. Of note, the SAP was not modified to reflect the presentation of the combination output.

The key analyses for all disease assessment-related endpoints were carried out on the derived response rate based on local morphology using the Safety Analysis Set, equivalent to a traditional Intent-To-Treat Analysis Set.

Protection of trial subjects:

This trial was conducted under ICH E6 Good Clinical Practices, which has its foundation in the Declaration of Helsinki. Subjects were allowed to continue taking the compound after trial completion, as long as it was providing benefit (compassionate use).

A single scheduled review of efficacy data was conducted by an independent Data Monitoring Committee (DMC) for recommendation whether to continue the study from the Exploratory Stage into the Confirmatory Stage. The DMC reviewed trial safety data in an ongoing fashion as detailed below.

The DMC was responsible for safeguarding the interests of study subjects, assessing the safety and efficacy of the interventions during the study, and for monitoring the overall conduct of the clinical study. The DMC was tasked with providing recommendations about stopping or continuing the study. The DMC was responsible for confirming the safety and related parameters including corrected QT interval (QTc) prolongation interval and primary response data to be monitored, as defined in the protocol, and discussed the frequency of DMC meetings and criteria for making recommendations to the Sponsor. Safety/study integrity reviews were held during protocol enrollment and follow-up, to review safety information, response data and factors relating to quality of study conduct. Because this was an open-label study, the DMC members were not blinded to a subject’s or a group’s treatment.

The DMC was advisory to the Sponsor. The Sponsor had the responsibility to promptly review the DMC recommendations, to decide whether to continue, modify or terminate the study, and to determine whether amendments to the protocol or changes in study conduct were required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	France: 53
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	United States: 145
Country: Number of subjects enrolled	Canada: 4
Worldwide total number of subjects	333
EEA total number of subjects	184

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)	186
From 65 to 84 years	145
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of all potential participants screened, a total of 333 patients were enrolled in nine countries.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Cohort 1 was to include subjects 60 years of age or older who relapsed within 1 year after first line chemotherapy regimen, with or without consolidation, or were primary refractory to first line chemotherapy.

- Exploratory (N=24): FLT3-ITD(+): n=22; FLT-ITD(-): n=2; unknown: n=0
- Confirmatory (N=133): FLT3-ITD(+): n=90; FLT-ITD(-): n=42; unknown: n=1
- Total (N=157): FLT3-ITD(+): n=112; FLT-ITD(-): n=44; unknown: n=1

Arm type	Experimental
Investigational medicinal product name	Quizartinib
Investigational medicinal product code	
Other name	Compound AC220
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Quizartinib administered as a once daily oral solution given continuously as 28-day treatment cycles, without any rest periods, until disease progression, relapse, intolerance to the drug, or elective allogeneic hematopoietic stem cell transplantation (HSCT)

Arm title	Cohort 2

Arm description:

Cohort 2 was to include subjects 18 years of age or older, including those 60 years of age or older, who were relapsed or refractory after 1 second line (salvage) regimen, or after hematopoietic stem cell transplant (HSCT).

- Exploratory (N=38): FLT3-ITD(+): n=36; FLT-ITD(-): n=2; unknown: n=0
- Confirmatory (N=138): FLT3-ITD(+): n=100; FLT-ITD(-): n=38; unknown: n=0
- Total (N=176): FLT3-ITD(+): n=136; FLT-ITD(-): n=40; unknown: n=0

Arm type	Experimental
Investigational medicinal product name	Quizartinib
Investigational medicinal product code	
Other name	Compound AC220
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Quizartinib administered as a once daily oral solution given continuously as 28-day treatment cycles, without any rest periods, until disease progression, relapse, intolerance to the drug, or elective allogeneic hematopoietic stem cell transplantation (HSCT)

Number of subjects in period 1	Cohort 1	Cohort 2
Started	157	176
Study Treatment Discontinued	155	174
Completed	142	154
Not completed	15	22
Consent withdrawn by subject	-	1
Lost to follow-up	3	-
Still in Follow-up	12	21

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1

Reporting group description:

Cohort 1 was to include subjects 60 years of age or older who relapsed within 1 year after first line chemotherapy regimen, with or without consolidation, or were primary refractory to first line chemotherapy.

- Exploratory (N=24): FLT3-ITD(+): n=22; FLT-ITD(-): n=2; unknown: n=0
- Confirmatory (N=133): FLT3-ITD(+): n=90; FLT-ITD(-): n=42; unknown: n=1
- Total (N=157): FLT3-ITD(+): n=112; FLT-ITD(-): n=44; unknown: n=1

Reporting group title	Cohort 2

Reporting group description:

Cohort 2 was to include subjects 18 years of age or older, including those 60 years of age or older, who were relapsed or refractory after 1 second line (salvage) regimen, or after hematopoietic stem cell transplant (HSCT).

- Exploratory (N=38): FLT3-ITD(+): n=36; FLT-ITD(-): n=2; unknown: n=0
- Confirmatory (N=138): FLT3-ITD(+): n=100; FLT-ITD(-): n=38; unknown: n=0
- Total (N=176): FLT3-ITD(+): n=136; FLT-ITD(-): n=40; unknown: n=0

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	157	176	333
Age categorical Units: Subjects			
less than 60 years	2	132	134
at least 60 years	155	44	199
Age continuous Units: years			
median	69.0	51.0	
full range (min-max)	32 to 86	19 to 77	-
Gender categorical Units: Subjects			
Female	80	83	163
Male	77	93	170
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	5	7
Black or African American	5	5	10
Native Hawaiian or Other Pacific Islander	1	0	1
White	135	156	291
Not Provided	12	4	16
Other	2	6	8
Ethnicity Units: Subjects			
Hispanic	4	6	10
Not Hispanic	126	150	276
Not allowed to ask per local regulations	27	20	47

Weight Units: kg			
arithmetic mean	74.66	74.76	
standard deviation	± 14.75	± 19.41	-

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

Cohort 1 was to include subjects 60 years of age or older who relapsed within 1 year after first line chemotherapy regimen, with or without consolidation, or were primary refractory to first line chemotherapy.

- Exploratory (N=24): FLT3-ITD(+): n=22; FLT-ITD(-): n=2; unknown: n=0
- Confirmatory (N=133): FLT3-ITD(+): n=90; FLT-ITD(-): n=42; unknown: n=1
- Total (N=157): FLT3-ITD(+): n=112; FLT-ITD(-): n=44; unknown: n=1

Reporting group title	Cohort 2

Reporting group description:

Cohort 2 was to include subjects 18 years of age or older, including those 60 years of age or older, who were relapsed or refractory after 1 second line (salvage) regimen, or after hematopoietic stem cell transplant (HSCT).

- Exploratory (N=38): FLT3-ITD(+): n=36; FLT-ITD(-): n=2; unknown: n=0
- Confirmatory (N=138): FLT3-ITD(+): n=100; FLT-ITD(-): n=38; unknown: n=0
- Total (N=176): FLT3-ITD(+): n=136; FLT-ITD(-): n=40; unknown: n=0

Primary: Derived Disease Assessment Based on Local Morphology Including All On-Treatment Data (Safety Population, FLT3-ITD (+) Subjects)

End point title	Derived Disease Assessment Based on Local Morphology Including All On-Treatment Data (Safety Population, FLT3-ITD (+) Subjects)[1]

End point description:

Derived disease assessment based on local morphology of bone marrow disease performed by each local site pathologist, including all on-treatment data (Safety Population, FLT3-ITD(+) Patients)

Modified from Cheson et al, abbreviations used include the following: CR = complete remission; CRc = composite complete remission (CR + CRp + CRi); CRi = complete remission with incomplete hematological recovery, includes subjects who met CRia criteria plus subjects who met CRib criteria; CRia = all criteria specified for CR are met except for incomplete hematological recovery with residual neutropenia <1 × 109/L with or without complete platelet recovery. Red blood cell and platelet transfusion independence is not required; CRib = All criteria for CR or CRp are met, except for recent red blood cell or platelet transfusion; CRp = complete remission with incomplete platelet recovery; NR = no response; PR = partial remission.

End point type	Primary

End point timeframe:

Within the first 3 cycles of treatment (84 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Comparisons between cohorts were not made.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	136		
Units: Patients				
CRc	63	62		
CR	3	5		
CRp	4	2		
CRi	56	55		

PR	23	39		
NR	20	24		
UNK	6	11		

Statistical analyses

No statistical analyses for this end point

Primary: Derived Disease Assessment Based on Local Morphology Including All On-Treatment Data (Safety Population, FLT3-ITD (-) Subjects)

End point title	Derived Disease Assessment Based on Local Morphology Including All On-Treatment Data (Safety Population, FLT3-ITD (-) Subjects)[2]

End point description:

Derived disease assessment based on local morphology of bone marrow disease performed by each local site pathologist, including all on-treatment data.

Modified from Cheson et al, abbreviations used include the following: CR = complete remission; CRc = composite complete remission (CR + CRp + CRi); CRi = complete remission with incomplete hematological recovery, includes subjects who met CRia criteria plus subjects who met CRib criteria; CRia = all criteria specified for CR are met, except for incomplete hematological recovery with residual neutropenia <1 × 109/L with or without complete platelet recovery. Red blood cell and platelet transfusion independence is not required; CRib = All criteria for CR or CRp are met, except for recent red blood cell or platelet transfusion; NR = no response; PR = partial remission; UNK = unknown

End point type	Primary

End point timeframe:

Within the first 3 cycles of treatment (84 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Comparisons between cohorts were not made.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	40		
Units: Patients				
CRc	16	12		
CR	2	1		
CRp	1	1		
CRi	13	10		
PR	4	6		
NR	17	16		
UNK	7	6		

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with composite complete remission (CRc), categorised by FLT3-ITD status

End point title	Number of patients with composite complete remission (CRc), categorised by FLT3-ITD status[3]

End point description:

CRc is defined as composite complete remission (CR + CRp + CRi) - CR = complete remission; CRp = complete remission with incomplete platelet recovery; CRi = complete remission with incomplete hematological recovery, includes subjects who met CRia criteria plus subjects who met CRib criteria; CRia = all criteria specified for CR are met except for incomplete hematological recovery with residual neutropenia <1 × 109/L with or without complete platelet recovery. Red blood cell and platelet transfusion independence is not required; CRib = All criteria for CR or CRp are met, except for recent red blood cell or platelet transfusion

End point type	Primary

End point timeframe:

within 28 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Comparisons between cohorts were not made.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	176		
Units: Patients				
FLT3-ITD (+)	63	62		
FLT3-ITD (-)	16	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Composite Complete Remission in Subjects who Achieved CRc Based on All On-Treatment Data

End point title	Duration of Composite Complete Remission in Subjects who Achieved CRc Based on All On-Treatment Data

End point description:

Kaplan-Meier analysis of duration of composite complete remission derived based on local morphology including all on-treatment data (Safety Population)

The definition of relapse at CRc includes an evaluation of blasts in the peripheral blood of >1%. Though not specified in the protocol, the addition of these criteria was deemed necessary for consistency with the Cheson criteria.

End point type	Secondary

End point timeframe:

Within first 3 cycles of treatment (84 days)

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[4]	62[5]		
Units: Weeks				
median (confidence interval 95%)				
FLT3-ITD(+) Patients	12.1 (6.3 to 15.7)	10.6 (8.1 to 16.1)		
FLT3-ITD(-) Patients	16.4 (8.1 to 30.4)	7.0 (4.1 to 8.1)		

Notes:

[4] - Note: N=63 for FLTE-ITD (+) subjects and N=16 for FLT3-ITD(-) subjects

[5] - Note: N=62 for FLTE-ITD (+) subjects and N=12 for FLT3-ITD(-) subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Any Response

End point title	Duration of Any Response

End point description:

Kaplan-Meier analysis of duration of any response (CR, CRp, CRi, or PR), derived based on local morphology for subjects who achieved a response during the first 3 cycles of treatment (Safety Population)

End point type	Secondary

End point timeframe:

Within the first 3 cycles of treatment (84 days)

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[6]	99[7]		
Units: Weeks				
median (confidence interval 95%)				
FLT3-ITD(+) Patients	15.1 (12.1 to 18.4)	12.1 (10.0 to 18.4)		
FLT3-ITD(-) Patients	12.4 (8.3 to 30.4)	7.9 (6.3 to 12.1)		

Notes:

[6] - Note: N=83 for FLTE-ITD (+) subjects and N=20 for FLT3-ITD(-) subjects

[7] - Note: N=99 for FLTE-ITD (+) subjects and N=18 for FLT3-ITD(-) subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Leukemia-Free Survival

End point title	Median Duration of Leukemia-Free Survival

End point description:

Kaplan-Meier analysis of leukemia-free survival in patients who achieved a CRc in the first three cycles of treatment derived based on local morphology (Safety Population)

End point type	Secondary

End point timeframe:
Within first 3 cycles of treatment (84 days)

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[8]	61[9]		
Units: Weeks				
median (confidence interval 95%)				
FLT3-ITD(+) Patients	12.1 (6.1 to 14.3)	12.9 (9.4 to 19.1)		
FLT3-ITD(-) Patients	20.4 (8.1 to 26.1)	7.0 (5.0 to 8.1)		

Notes:
[8] - Note: N=61 for FLTE-ITD (+) subjects and N=13 for FLT3-ITD(-) subjects
[9] - Note: N=61 for FLTE-ITD (+) subjects and N=11 for FLT3-ITD(-) subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Overall Survival

End point title	Median Duration of Overall Survival

End point description:
Kaplan-Meier analysis of overall survival (Safety population)

End point type	Secondary

End point timeframe:
Within first 3 cycles of treatment (84 days)

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112[10]	136[11]		
Units: weeks				
number (confidence interval 95%)				
FLTE-ITD (+) Subjects	25.4 (21.3 to 29.7)	24.0 (21.1 to 27.1)		
FLTE-ITD (-) Subjects	19.1 (12.0 to 29.4)	25.1 (18.1 to 37.0)		

Notes:
[10] - Note: N=112 for FLTE-ITD (+) subjects and N=44 for FLT3-ITD(-) subjects
[11] - Note: N=136 for FLTE-ITD (+) subjects and N=40 for FLT3-ITD(-) subjects

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the trial plus 30 days	
Adverse event reporting additional description:	
Of note, AML disease progression (which includes the verbatim terms of progressive disease, disease progression, and relapsed AML) is reported as an AE in the data output and in the in-text tables; however, it is not considered an AE because of the subject population under study and is not further discussed.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	Cohort 1
Reporting group description: -	
Reporting group title	Cohort 2
Reporting group description: -	

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	134 / 157 (85.35%)	135 / 176 (76.70%)	
number of deaths (all causes)	71	60	
number of deaths resulting from adverse events	10	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	37 / 157 (23.57%)	36 / 176 (20.45%)	
occurrences causally related to treatment / all	0 / 37	0 / 36	
deaths causally related to treatment / all	0 / 35	0 / 32	
Leukaemic infiltration brain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphohistiocytosis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelofibrosis			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 157 (0.64%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypotension			
subjects affected / exposed	3 / 157 (1.91%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 157 (1.27%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Fatigue			
subjects affected / exposed	1 / 157 (0.64%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 157 (1.27%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	1 / 1	0 / 1	
Localised oedema			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Oedema peripheral			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	10 / 157 (6.37%)	8 / 176 (4.55%)	
occurrences causally related to treatment / all	5 / 10	4 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
Secretion discharge			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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			
Graft versus host disease in skin			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
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	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute promyelocytic leukaemia differentiation syndrome			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 157 (0.64%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 157 (1.27%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 157 (1.27%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	3 / 157 (1.91%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 157 (0.64%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	1 / 157 (0.64%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	17 / 157 (10.83%)	16 / 176 (9.09%)	
occurrences causally related to treatment / all	17 / 17	15 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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			
Accidental overdose			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Accidental poisoning			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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	3 / 157 (1.91%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 157 (5.10%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	6 / 8	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 157 (0.64%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Cardiac failure			
subjects affected / exposed	3 / 157 (1.91%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 157 (1.27%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsade de pointes			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lesion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 157 (1.27%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 157 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	4 / 157 (2.55%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Haemorrhagic stroke			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	2 / 157 (1.27%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Memory impairment			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postictal state			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 157 (1.27%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 157 (4.46%)	6 / 176 (3.41%)	
occurrences causally related to treatment / all	5 / 7	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile bone marrow aplasia			
subjects affected / exposed	4 / 157 (2.55%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	60 / 157 (38.22%)	66 / 176 (37.50%)	
occurrences causally related to treatment / all	34 / 60	42 / 66	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	2 / 157 (1.27%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 157 (0.64%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancytopenia			
subjects affected / exposed	1 / 157 (0.64%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombocytopenia			
subjects affected / exposed	4 / 157 (2.55%)	6 / 176 (3.41%)	
occurrences causally related to treatment / all	3 / 4	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 157 (1.27%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Barrett's oesophagus			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 157 (1.91%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	1 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal incontinence			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 157 (2.55%)	7 / 176 (3.98%)	
occurrences causally related to treatment / all	1 / 4	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestine perforation			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 157 (0.64%)	5 / 176 (2.84%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 157 (0.64%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 157 (2.55%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 157 (1.27%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	1 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 157 (0.64%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 157 (0.64%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petechiae			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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	3 / 157 (1.91%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 157 (1.27%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal tubular disorder			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	2 / 157 (1.27%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	6 / 157 (3.82%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	0 / 6	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial sepsis			
subjects affected / exposed	2 / 157 (1.27%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Breast cellulitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 157 (1.27%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Candidiasis			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 157 (1.27%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Influenza			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	2 / 157 (1.27%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 157 (0.64%)	6 / 176 (3.41%)	
occurrences causally related to treatment / all	1 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung infection pseudomonal			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericoronitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	24 / 157 (15.29%)	16 / 176 (9.09%)	
occurrences causally related to treatment / all	7 / 24	7 / 16	
deaths causally related to treatment / all	2 / 6	0 / 1	
Pneumonia fungal			
subjects affected / exposed	1 / 157 (0.64%)	7 / 176 (3.98%)	
occurrences causally related to treatment / all	0 / 1	2 / 7	
deaths causally related to treatment / all	0 / 0	1 / 3	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (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	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection fungal			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rhinovirus infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	12 / 157 (7.64%)	13 / 176 (7.39%)	
occurrences causally related to treatment / all	5 / 12	3 / 13	
deaths causally related to treatment / all	1 / 3	1 / 6	
Sepsis syndrome			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic shock			

subjects affected / exposed	3 / 157 (1.91%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	1 / 2	0 / 1	
Serratia bacteraemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	2 / 157 (1.27%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	6 / 157 (3.82%)	6 / 176 (3.41%)	
occurrences causally related to treatment / all	1 / 6	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 157 (1.27%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cellulitis			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			

subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 157 (0.64%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 157 (3.18%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 157 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 157 (0.64%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 157 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 157 (0.64%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	151 / 157 (96.18%)	175 / 176 (99.43%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	17 / 157 (10.83%)	12 / 176 (6.82%)	
occurrences (all)	17	12	
Hypotension			
subjects affected / exposed	17 / 157 (10.83%)	13 / 176 (7.39%)	
occurrences (all)	17	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	33 / 157 (21.02%)	32 / 176 (18.18%)	
occurrences (all)	33	32	
Chest pain			
subjects affected / exposed	10 / 157 (6.37%)	13 / 176 (7.39%)	
occurrences (all)	10	13	
Chills			
subjects affected / exposed	13 / 157 (8.28%)	14 / 176 (7.95%)	
occurrences (all)	13	14	
Fatigue			

subjects affected / exposed	62 / 157 (39.49%)	49 / 176 (27.84%)	
occurrences (all)	62	49	
Mucosal inflammation			
subjects affected / exposed	8 / 157 (5.10%)	15 / 176 (8.52%)	
occurrences (all)	8	15	
Oedema peripheral			
subjects affected / exposed	46 / 157 (29.30%)	45 / 176 (25.57%)	
occurrences (all)	46	45	
Pyrexia			
subjects affected / exposed	47 / 157 (29.94%)	49 / 176 (27.84%)	
occurrences (all)	47	49	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 157 (16.56%)	37 / 176 (21.02%)	
occurrences (all)	26	37	
Dyspnoea			
subjects affected / exposed	28 / 157 (17.83%)	26 / 176 (14.77%)	
occurrences (all)	28	26	
Dyspnoea exertional			
subjects affected / exposed	8 / 157 (5.10%)	2 / 176 (1.14%)	
occurrences (all)	8	2	
Epistaxis			
subjects affected / exposed	29 / 157 (18.47%)	27 / 176 (15.34%)	
occurrences (all)	29	27	
Oropharyngeal pain			
subjects affected / exposed	8 / 157 (5.10%)	10 / 176 (5.68%)	
occurrences (all)	8	10	
Pleural effusion			
subjects affected / exposed	8 / 157 (5.10%)	12 / 176 (6.82%)	
occurrences (all)	8	12	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	8 / 157 (5.10%)	2 / 176 (1.14%)	
occurrences (all)	8	2	
Depression			

subjects affected / exposed	12 / 157 (7.64%)	10 / 176 (5.68%)	
occurrences (all)	12	10	
Insomnia			
subjects affected / exposed	11 / 157 (7.01%)	15 / 176 (8.52%)	
occurrences (all)	11	15	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 157 (5.73%)	15 / 176 (8.52%)	
occurrences (all)	9	15	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 157 (5.10%)	7 / 176 (3.98%)	
occurrences (all)	8	7	
Electrocardiogram QT prolonged			
subjects affected / exposed	31 / 157 (19.75%)	48 / 176 (27.27%)	
occurrences (all)	31	48	
Neutrophil count decreased			
subjects affected / exposed	8 / 157 (5.10%)	6 / 176 (3.41%)	
occurrences (all)	8	6	
Platelet count decreased			
subjects affected / exposed	17 / 157 (10.83%)	12 / 176 (6.82%)	
occurrences (all)	17	12	
Weight decreased			
subjects affected / exposed	10 / 157 (6.37%)	11 / 176 (6.25%)	
occurrences (all)	10	11	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	14 / 157 (8.92%)	6 / 176 (3.41%)	
occurrences (all)	14	6	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	10 / 157 (6.37%)	10 / 176 (5.68%)	
occurrences (all)	10	10	
Nervous system disorders			
Dizziness			
subjects affected / exposed	27 / 157 (17.20%)	18 / 176 (10.23%)	
occurrences (all)	27	18	

Dysgeusia			
subjects affected / exposed	44 / 157 (28.03%)	34 / 176 (19.32%)	
occurrences (all)	44	34	
Headache			
subjects affected / exposed	19 / 157 (12.10%)	24 / 176 (13.64%)	
occurrences (all)	19	24	
Paraesthesia			
subjects affected / exposed	13 / 157 (8.28%)	5 / 176 (2.84%)	
occurrences (all)	13	5	
Tremor			
subjects affected / exposed	10 / 157 (6.37%)	2 / 176 (1.14%)	
occurrences (all)	10	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	44 / 157 (28.03%)	48 / 176 (27.27%)	
occurrences (all)	44	48	
Febrile neutropenia			
subjects affected / exposed	12 / 157 (7.64%)	14 / 176 (7.95%)	
occurrences (all)	12	14	
Leukopenia			

subjects affected / exposed	24 / 157 (15.29%)	3 / 176 (1.70%)	
occurrences (all)	24	3	
Constipation			
subjects affected / exposed	35 / 157 (22.29%)	36 / 176 (20.45%)	
occurrences (all)	35	36	
Diarrhoea			
subjects affected / exposed	65 / 157 (41.40%)	67 / 176 (38.07%)	
occurrences (all)	65	67	
Dry mouth			
subjects affected / exposed	8 / 157 (5.10%)	2 / 176 (1.14%)	
occurrences (all)	8	2	
Dyspepsia			
subjects affected / exposed	29 / 157 (18.47%)	25 / 176 (14.20%)	
occurrences (all)	29	25	
Gastrooesophageal reflux disease			
subjects affected / exposed	16 / 157 (10.19%)	9 / 176 (5.11%)	
occurrences (all)	16	9	
Gingival bleeding			
subjects affected / exposed	6 / 157 (3.82%)	9 / 176 (5.11%)	
occurrences (all)	6	9	
Haemorrhoids			
subjects affected / exposed	10 / 157 (6.37%)	9 / 176 (5.11%)	
occurrences (all)	10	9	
Mouth haemorrhage			
subjects affected / exposed	12 / 157 (7.64%)	10 / 176 (5.68%)	
occurrences (all)	12	10	
Nausea			
subjects affected / exposed	85 / 157 (54.14%)	89 / 176 (50.57%)	
occurrences (all)	85	89	
Stomatitis			
subjects affected / exposed	9 / 157 (5.73%)	7 / 176 (3.98%)	
occurrences (all)	9	7	
Vomiting			
subjects affected / exposed	57 / 157 (36.31%)	70 / 176 (39.77%)	
occurrences (all)	57	70	
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	8 / 157 (5.10%)	9 / 176 (5.11%)	
occurrences (all)	8	9	
Erythema			
subjects affected / exposed	11 / 157 (7.01%)	14 / 176 (7.95%)	
occurrences (all)	11	14	
Hair colour changes			
subjects affected / exposed	3 / 157 (1.91%)	9 / 176 (5.11%)	
occurrences (all)	3	9	
Petechiae			
subjects affected / exposed	32 / 157 (20.38%)	29 / 176 (16.48%)	
occurrences (all)	32	29	
Pruritus			
subjects affected / exposed	8 / 157 (5.10%)	9 / 176 (5.11%)	
occurrences (all)	8	9	
Rash			
subjects affected / exposed	22 / 157 (14.01%)	24 / 176 (13.64%)	
occurrences (all)	22	24	
Skin lesion			
subjects affected / exposed	7 / 157 (4.46%)	12 / 176 (6.82%)	
occurrences (all)	7	12	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	10 / 157 (6.37%)	9 / 176 (5.11%)	
occurrences (all)	10	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 157 (8.92%)	8 / 176 (4.55%)	
occurrences (all)	14	8	
Back pain			
subjects affected / exposed	19 / 157 (12.10%)	17 / 176 (9.66%)	
occurrences (all)	19	17	
Bone pain			
subjects affected / exposed	11 / 157 (7.01%)	4 / 176 (2.27%)	
occurrences (all)	11	4	
Muscle spasms			

subjects affected / exposed	16 / 157 (10.19%)	10 / 176 (5.68%)	
occurrences (all)	16	10	
Musculoskeletal pain			
subjects affected / exposed	12 / 157 (7.64%)	12 / 176 (6.82%)	
occurrences (all)	12	12	
Myalgia			
subjects affected / exposed	7 / 157 (4.46%)	14 / 176 (7.95%)	
occurrences (all)	7	14	
Neck pain			
subjects affected / exposed	10 / 157 (6.37%)	4 / 176 (2.27%)	
occurrences (all)	10	4	
Pain in extremity			
subjects affected / exposed	17 / 157 (10.83%)	22 / 176 (12.50%)	
occurrences (all)	17	22	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	9 / 157 (5.73%)	10 / 176 (5.68%)	
occurrences (all)	9	10	
Oral herpes			
subjects affected / exposed	12 / 157 (7.64%)	9 / 176 (5.11%)	
occurrences (all)	12	9	
Pneumonia			
subjects affected / exposed	2 / 157 (1.27%)	15 / 176 (8.52%)	
occurrences (all)	2	15	
Sinusitis			
subjects affected / exposed	3 / 157 (1.91%)	9 / 176 (5.11%)	
occurrences (all)	3	9	
Urinary tract infection			
subjects affected / exposed	9 / 157 (5.73%)	8 / 176 (4.55%)	
occurrences (all)	9	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	46 / 157 (29.30%)	43 / 176 (24.43%)	
occurrences (all)	46	43	
Hyperglycaemia			

subjects affected / exposed	13 / 157 (8.28%)	11 / 176 (6.25%)	
occurrences (all)	13	11	
Hypocalcaemia			
subjects affected / exposed	15 / 157 (9.55%)	18 / 176 (10.23%)	
occurrences (all)	15	18	
Hypokalaemia			
subjects affected / exposed	27 / 157 (17.20%)	33 / 176 (18.75%)	
occurrences (all)	27	33	
Hypomagnesaemia			
subjects affected / exposed	17 / 157 (10.83%)	19 / 176 (10.80%)	
occurrences (all)	17	19	
Hyponatraemia			
subjects affected / exposed	7 / 157 (4.46%)	9 / 176 (5.11%)	
occurrences (all)	7	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2009	No patients were enrolled under the original protocol nor this first amendment. The reasons for this amendment were to: - Delete limitation on Second Complete Remission duration for inclusion of subjects in second relapse - Clarify dosing adjustments for subjects with nonhaematological toxicities - Clarify pharmacokinetic (PK) and pharmacodynamic (PD) sampling
22 July 2009	This amendment was written to: - Exclude subjects with other cancers (except treated Stage 1 cervix or nonmelanotic skin cancer) with the possible exception of subjects in complete remission - Include subjects with controlled CNS leukemia receiving IT therapy - Clarify that the use of other chemotherapeutic or antileukemic agents is not permitted during the study with the exception of hydroxyurea and possible exception of IT therapy (based on investigator discretion and Sponsor agreement). - Add multigated acquisition scan (MUGA) for assessment of left ventricular ejection fraction (LVEF), change the requirement of assessment of LVEF from 3 months to 1 month before study screening to enhance subject safety. - Clarify the role of the independent DMC to include assessment of risk versus benefit and recommend any changes warranted to the study design. - Add 30-day and 3-month telephone follow-up after end of study for safety assessments, further therapies, outcomes and survival in order to record protocol-specified data - Add other genotyping and mRNA analyses to the blood and bone marrow assessments in order to ensure all such assessments are properly described in the protocol.

16 November 2009	• Increase the maximum number of study sites from ~80 to ~100. • Add "Time to treatment response" as another secondary objective. • Predefined a mutant ratio of >10% FLT3-ITD mutant alleles as a criteria for inclusion in the study. • Require that appropriate samples of bone marrow taken for diagnosis before the subject signs consent and within 14 days prior to first dose of study drug be sent to the Sponsor's designated laboratory for later morphological confirmation of the AML diagnosis if the bone marrow testing is not repeated during screening. • Specify that bone marrow aspirates and biopsies are preferred, but biopsies may be omitted at the discretion of the Investigator if an adequate aspirate is obtained. • Specify that screening procedures are to be performed ≤14 days from Cycle 1Day 1. • Specify that donor lymphocyte infusion is not permitted during study or 30 days prior to study entry. • Specify the option of a further dose reduction to 90 mg as appropriate. • Specify replacement criteria for subjects erroneously entered into the study. • Allow for MUGA or ECHO at the Screening visit for subjects with current or history of congestive heart failure NYHA class 3 or 4, unless an ECHO or MUGA performed either within 1 month prior to study screening or during screening results in a LVEF that is ≥45% (or institutional lower limit of normal value). • Add language to make the ECG and PK blood draw sequence less restrictive • Add phosphate to clinical laboratory tests. • Add provision for the possibility of stopping for futility based on efficacy at interim timepoints as incorporated in the DMC Charter. • Amend language; reference to disease progression and progressive disease were changed to relapse or deleted if relapse was already stated.
20 April 2010	In Study AC220-002, the co-primary objectives are to determine complete remission (CR) rate and composite complete remission (CRc) rate, which is the sum of CR, CR with incomplete platelet response (CRp), and CR with incomplete hematological response (CRi). The original intent of the protocol was to use a modified set of Cheson criteria for the assessment of clinical response for efficacy. Specifically, the need for red blood cell (RBC) or platelet transfusions was not to be taken into account for declaring responses of CRi. All of the other Cheson criteria for defining CR, CRp, and CRi were to remain unchanged [34]. This modification was to be implemented in order to fully describe the antileukemic activity of AC220, which is given as a continuous therapy and is myelosuppressive. Previous versions of the protocol erroneously omitted this modification; therefore, Protocol Amendment 7 has been written to clarify the use of the modified Cheson criteria and specify that patients do not need to be RBC or platelet transfusion independent in order for their response to be classified as CRi. An additional change to the protocol has been made for the evaluation of best response. Previous versions of the protocol indicated that best response will be measured up to Day 84 (after 3 cycles of therapy), or at time off study for those patients discontinuing treatment before Day 84. As described in Protocol Amendment 7, best response will also be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

05 November 2010	The primary reason for Protocol Amendment 5 is to provide dose modification guidelines for patients who experience complete remission (CR) with incomplete platelet recovery (CRp) or incomplete neutrophil recovery, with or without complete platelet recovery (CRi). Patients experiencing prolonged CRi or CRp may be dose reduced at the discretion of the Investigator and with agreement of the Sponsor. The following criteria must be met: < 100 x 109/L platelets and/or ≤ 1 x 109/L absolute neutrophil count (ANC); marrow blasts < 5%; and the patient has received at least 2 cycles of study treatment. Dose reduction will proceed in a stepwise fashion to a minimum of 60 mg/day (ie, 200 mg/day to 135 mg/day to 90 mg/day to 60 mg/day) if myelosuppression persists and there is no evidence of AML relapse. After any dose reduction, patients should receive at least one complete cycle (28 days) of the reduced dose before further dose reduction is implemented. Patients who subsequently lose response (ie, relapse) may be dose escalated as described in the protocol.
08 January 2011	Introduction was updated and secondary objectives were changed as follows: Changed from: • Pharmacogenetic analysis of FLT3-ITD mutation • Correlation of remission with FLT3-ITD allelic ratio and other parameters using other assays Changed to: • Pharmacogenetic analysis of FLT3-ITD mutation • For all patients with detectable FLT3-ITD mutation, correlation of remission with FLT3-ITD allelic ratio and other parameters using other assays • For all patients, summaries of non-ITD mutations identified, the percent mutant allelic ratio (normalized for blasts), and correlational analyses.
15 July 2011	In Study AC220-002, the co-primary objectives are to determine complete remission (CR) rate and composite complete remission (CRc) rate, which is the sum of CR, CR with incomplete platelet response (CRp), and CR with incomplete hematological response (CRi). The original intent of the protocol was to use a modified set of Cheson criteria for the assessment of clinical response for efficacy. Specifically, the need for red blood cell (RBC) or platelet transfusions was not to be taken into account for declaring responses of CRi. All of the other Cheson criteria for defining CR, CRp, and CRi were to remain unchanged [34]. This modification was to be implemented in order to fully describe the antileukemic activity of AC220, which is given as a continuous therapy and is myelosuppressive. Previous versions of the protocol erroneously omitted this modification; therefore, Protocol Amendment 7 has been written to clarify the use of the modified Cheson criteria and specify that patients do not need to be RBC or platelet transfusion independent in order for their response to be classified as CRi. An additional change to the protocol has been made for the evaluation of best response. Previous versions of the protocol indicated that best response will be measured up to Day 84 (after 3 cycles of therapy), or at time off study for those patients discontinuing treatment before Day 84. As described in Protocol Amendment 7, best response will also be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported