

**Clinical trial results:****A Phase 3 Open-Label Randomized Study of Quizartinib Monotherapy Versus Salvage Chemotherapy in Subjects with FLT3-ITD Positive Acute Myeloid Leukemia (AML) Refractory to or Relapsed after First-Line Treatment with or without Hematopoietic Stem Cell Transplantation (HSCT) Consolidation****Summary**

EudraCT number	2013-004890-28
Trial protocol	GB DE IT NL ES BE HU CZ HR PL
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	27 May 2020
First version publication date	22 March 2019
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Outcome measures are updated. Study data as of cut-off date (22 February 2018) are the defined study end point in the protocol.

Trial information**Trial identification**

Sponsor protocol code	AC220-007
-----------------------	-----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02039726
WHO universal trial number (UTN)	U1111-1151-8078

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, After May 1, 2017, 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	Interim
Date of interim/final analysis	22 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine whether quizartinib monotherapy prolongs overall survival (OS) compared to salvage chemotherapy in subjects with FLT3-ITD positive AML who are refractory to or have relapsed within 6 months, after first-line AML therapy.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	31 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	United States: 118
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Singapore: 2

Country: Number of subjects enrolled	Taiwan: 3
Worldwide total number of subjects	367
EEA total number of subjects	188

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)	269
From 65 to 84 years	98
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 367 patients who met the inclusion and none of the exclusion criteria were randomized (intent-to-treat population); 335 received study drug (Safety Analysis Set). A total of 32 patients (n=4 Quizartinib; n=28 salvage chemotherapy) did not receive treatment.

Pre-assignment

Screening details:

Prior to randomization, the investigator was required to pre-select 1 of the 3 salvage chemotherapy regimens for each patient. Randomization was stratified by response to prior therapy (relapsed in ≤ 6 months [with or without HSCT] or refractory) and pre-selected salvage chemotherapy (high or low intensity chemotherapy) for all patients.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Quizartinib

Arm description:

Patients who were randomized to receive 20 or 30 mg Quizartinib tablets administered orally once daily.

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

Dosage and administration details:

Tablet; 30 mg and 20 mg, Oral tablets for daily administration

Arm title	Salvage chemotherapy
------------------	----------------------

Arm description:

Patients who were randomized to receive salvage chemotherapy, such as low dose cytarabine (LoDAC); mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin (FLAG-IDA), were administered during 28-day cycles.

Arm type	Active comparator
Investigational medicinal product name	Salvage chemotherapy
Investigational medicinal product code	
Other name	Standard of care
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Solution for intravenous (IV) or subcutaneous (SC) administration.

Standard of care, using commercially available product, per product packaging, including:

- low dose cytarabine (LoDAC);
- mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or
- fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin (FLAG-IDA).

Number of subjects in period 1	Quizartinib	Salvage chemotherapy
Started	245	122
Completed	200	106
Not completed	45	16
Still on Study	45	16

Baseline characteristics

Reporting groups

Reporting group title	Quizartinib
-----------------------	-------------

Reporting group description:

Patients who were randomized to receive 20 or 30 mg Quizartinib tablets administered orally once daily.

Reporting group title	Salvage chemotherapy
-----------------------	----------------------

Reporting group description:

Patients who were randomized to receive salvage chemotherapy, such as low dose cytarabine (LoDAC); mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin (FLAG-IDA), were administered during 28-day cycles.

Reporting group values	Quizartinib	Salvage chemotherapy	Total
Number of subjects	245	122	367
Age categorical			
Units: Subjects			
Adults (18-64 years)	180	89	269
From 65-84 years	65	33	98
Age continuous			
Median Age in Years			
Units: years			
median	55.0	57.5	
full range (min-max)	19 to 81	18 to 78	-
Gender categorical			
Units: Subjects			
Female	132	58	190
Male	113	64	177
Race			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	24	16	40
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	3	12
White	184	93	277
More than one race	0	0	0
Unknown or Not Reported	27	10	37

End points

End points reporting groups

Reporting group title	Quizartinib
Reporting group description: Patients who were randomized to receive 20 or 30 mg Quizartinib tablets administered orally once daily.	
Reporting group title	Salvage chemotherapy
Reporting group description: Patients who were randomized to receive salvage chemotherapy, such as low dose cytarabine (LoDAC); mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin (FLAG-IDA), were administered during 28-day cycles.	

Primary: Overall Survival in Patients That Received Quizartinib Versus Salvage Chemotherapy

End point title	Overall Survival in Patients That Received Quizartinib Versus Salvage Chemotherapy
End point description: Overall survival was assessed in the Intent-to-treat analysis set is defined as the time (in weeks) from the date of randomization to the date of death due to any cause. Median and quartiles are calculated using the Kaplan-Meier method.	
End point type	Primary
End point timeframe: At approximately 3 years, 9 months	

End point values	Quizartinib	Salvage chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	122		
Units: weeks				
median (inter-quartile range (Q1-Q3))	27.0 (15.4 to 62.6)	20.4 (8.3 to 39.6)		

Statistical analyses

Statistical analysis title	Hazard Ratio (Relative to Salvage Chemotherapy)
Statistical analysis description: Stratified analysis - stratification factors include prior therapy and response (Relapsed in ≤ 6 months (not post-HSCT), Refractory, or relapsed in ≤ 6 months post allogeneic HSCT), and pre-selected chemotherapy (High intensity chemotherapy [MEC or FLAG-IDA], or low intensity chemotherapy [LoDAC])	
Comparison groups	Quizartinib v Salvage chemotherapy

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0185
Method	p-value for HR=1 (1-Sided)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.758
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.584
upper limit	0.983

Secondary: Event-free survival in Patients That Received Quizartinib Versus Salvage Chemotherapy

End point title	Event-free survival in Patients That Received Quizartinib Versus Salvage Chemotherapy
End point description: Event-free survival was assessed in the Intent-to-treat analysis set and is defined as the time (in weeks) from randomization until documented refractory disease, relapse after complete composite remission (CRc), or death from any cause, whichever is observed first.	
End point type	Secondary
End point timeframe: At approximately 3 years, 9 months	

End point values	Quizartinib	Salvage chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	122		
Units: weeks				
median (inter-quartile range (Q1-Q3))	6.0 (0.1 to 19.7)	3.7 (0.1 to 17.0)		

Statistical analyses

Statistical analysis title	Hazard Ratio (Relative to Salvage Chemotherapy)
Statistical analysis description: Stratified analysis - Stratification factors include prior therapy and response (Relapsed in ≤6 months not post-HSCT, Refractory, or relapsed in ≤6 months post allogeneic HSCT), and pre-selected chemotherapy (high intensity chemotherapy [MEC or FLAG-IDA], or low intensity chemotherapy [LoDAC]).	
Comparison groups	Quizartinib v Salvage chemotherapy

Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2034
Method	p-value for HR=1 (1-sided)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.898
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.697
upper limit	1.157

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events (TEAEs) were collected from the first dose of study drug to 30 days after the last dose (or longer if assessed as treatment related). All safety events are reported for patients in the Safety Analysis Set.

Adverse event reporting additional description:

Differences in treatment regimens make the TEAE collection period span multiple 28-day cycles in the quizartinib arm and only 1-2 weeks in the salvage chemotherapy arm. .

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.1
--------------------	------

Reporting groups

Reporting group title	Quizartinib
-----------------------	-------------

Reporting group description:

Patients who were randomized to receive 20 or 30 mg Quizartinib tablets administered orally once daily.

Reporting group title	Salvage chemotherapy
-----------------------	----------------------

Reporting group description:

Patients who were randomized to receive salvage chemotherapy, such as low dose cytarabine (LoDAC); mitoxantrone, etoposide, and intermediate-dose cytarabine (MEC); or fludarabine, cytarabine, and granulocyte colony stimulating factor (G-CSF) with idarubicin (FLAG-IDA), were administered during 28-day cycles.

Serious adverse events	Quizartinib	Salvage chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	168 / 241 (69.71%)	37 / 94 (39.36%)	
number of deaths (all causes)	80	16	
number of deaths resulting from adverse events	36	11	
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	1 / 241 (0.41%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 241 (3.32%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	2 / 9	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular complication associated with device			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease in intestine			

subjects affected / exposed	4 / 241 (1.66%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Graft versus host disease in liver			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in skin			
subjects affected / exposed	3 / 241 (1.24%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 241 (0.41%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung disorder			
subjects affected / exposed	1 / 241 (0.41%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pleural effusion			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonitis			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 241 (0.41%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			

Depression			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	5 / 241 (2.07%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar vertebral fracture			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transfusion reaction			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 myocardial infarction			
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cognitive disorder			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	5 / 241 (2.07%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 1	
Headache			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Horner's syndrome			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 241 (2.07%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	6 / 241 (2.49%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	4 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	50 / 241 (20.75%)	9 / 94 (9.57%)	
occurrences causally related to treatment / all	21 / 65	6 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	2 / 241 (0.83%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 241 (1.66%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	3 / 241 (1.24%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 241 (1.24%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	0 / 94 (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	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	0 / 241 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	0 / 94 (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	5 / 241 (2.07%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 241 (2.07%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
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	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petechiae			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma gangrenosum			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	6 / 241 (2.49%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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			
Acarodermatitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anal infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	4 / 241 (1.66%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Candida infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	6 / 241 (2.49%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	3 / 241 (1.24%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	3 / 241 (1.24%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enterocolitis infectious		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia bacteraemia		
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia sepsis		
subjects affected / exposed	2 / 241 (0.83%)	3 / 94 (3.19%)
occurrences causally related to treatment / all	0 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Fungal skin infection		
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	3 / 241 (1.24%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis rotavirus		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis A		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.83%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Klebsiella sepsis		
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	1 / 241 (0.41%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		
subjects affected / exposed	3 / 241 (1.24%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0
Lymph gland infection		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Necrotising fasciitis		
subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1
Neutropenic infection		
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neutropenic sepsis		

subjects affected / exposed	7 / 241 (2.90%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	4 / 12	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Peritonitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	22 / 241 (9.13%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 24	1 / 3	
deaths causally related to treatment / all	0 / 7	0 / 1	
Pneumonia fungal			
subjects affected / exposed	3 / 241 (1.24%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mycosis			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis acute		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	1 / 241 (0.41%)	0 / 94 (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 viral		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	16 / 241 (6.64%)	4 / 94 (4.26%)
occurrences causally related to treatment / all	6 / 16	1 / 4
deaths causally related to treatment / all	1 / 2	0 / 0
Septic shock		
subjects affected / exposed	5 / 241 (2.07%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 6	1 / 1
deaths causally related to treatment / all	0 / 2	1 / 1
Sinusitis		
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Skin infection		
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Soft tissue infection		

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 241 (0.83%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	4 / 241 (1.66%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 241 (2.07%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	6 / 241 (2.49%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (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	Quizartinib	Salvage chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 241 (98.76%)	91 / 94 (96.81%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 241 (3.73%)	8 / 94 (8.51%)	
occurrences (all)	9	8	
Hypotension			
subjects affected / exposed	32 / 241 (13.28%)	10 / 94 (10.64%)	
occurrences (all)	39	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	34 / 241 (14.11%)	10 / 94 (10.64%)	
occurrences (all)	38	11	
Chills			
subjects affected / exposed	15 / 241 (6.22%)	7 / 94 (7.45%)	
occurrences (all)	15	8	
Fatigue			
subjects affected / exposed	67 / 241 (27.80%)	18 / 94 (19.15%)	
occurrences (all)	81	22	
Oedema peripheral			
subjects affected / exposed	51 / 241 (21.16%)	22 / 94 (23.40%)	
occurrences (all)	58	26	
Pain			

subjects affected / exposed occurrences (all)	19 / 241 (7.88%) 21	8 / 94 (8.51%) 8	
Pyrexia subjects affected / exposed occurrences (all)	88 / 241 (36.51%) 130	42 / 94 (44.68%) 69	
Immune system disorders			
Graft versus host disease subjects affected / exposed occurrences (all)	14 / 241 (5.81%) 14	0 / 94 (0.00%) 0	
Graft versus host disease in skin subjects affected / exposed occurrences (all)	16 / 241 (6.64%) 18	0 / 94 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	56 / 241 (23.24%) 64	13 / 94 (13.83%) 14	
Dyspnoea subjects affected / exposed occurrences (all)	48 / 241 (19.92%) 61	8 / 94 (8.51%) 11	
Epistaxis subjects affected / exposed occurrences (all)	28 / 241 (11.62%) 34	8 / 94 (8.51%) 9	
Nasal congestion subjects affected / exposed occurrences (all)	9 / 241 (3.73%) 9	5 / 94 (5.32%) 5	
Oropharyngeal pain subjects affected / exposed occurrences (all)	25 / 241 (10.37%) 26	6 / 94 (6.38%) 7	
Pleural effusion subjects affected / exposed occurrences (all)	14 / 241 (5.81%) 14	2 / 94 (2.13%) 2	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	19 / 241 (7.88%) 21	4 / 94 (4.26%) 4	
Confusional state			

subjects affected / exposed occurrences (all)	7 / 241 (2.90%) 7	5 / 94 (5.32%) 5	
Insomnia subjects affected / exposed occurrences (all)	22 / 241 (9.13%) 24	13 / 94 (13.83%) 13	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	32 / 241 (13.28%) 46	4 / 94 (4.26%) 5	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	26 / 241 (10.79%) 41	1 / 94 (1.06%) 1	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	18 / 241 (7.47%) 24	4 / 94 (4.26%) 5	
Blood bilirubin increased subjects affected / exposed occurrences (all)	24 / 241 (9.96%) 30	3 / 94 (3.19%) 6	
Blood creatinine increased subjects affected / exposed occurrences (all)	16 / 241 (6.64%) 22	2 / 94 (2.13%) 2	
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	63 / 241 (26.14%) 90	2 / 94 (2.13%) 2	
Neutrophil count decreased subjects affected / exposed occurrences (all)	31 / 241 (12.86%) 46	14 / 94 (14.89%) 21	
Platelet count decreased subjects affected / exposed occurrences (all)	33 / 241 (13.69%) 39	12 / 94 (12.77%) 20	
Weight decreased subjects affected / exposed occurrences (all)	27 / 241 (11.20%) 31	5 / 94 (5.32%) 5	
White blood cell count decreased			

subjects affected / exposed occurrences (all)	35 / 241 (14.52%) 45	14 / 94 (14.89%) 17	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	15 / 241 (6.22%) 17	2 / 94 (2.13%) 2	
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	8 / 241 (3.32%) 8	5 / 94 (5.32%) 5	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	36 / 241 (14.94%) 41	10 / 94 (10.64%) 10	
Dysgeusia subjects affected / exposed occurrences (all)	22 / 241 (9.13%) 22	1 / 94 (1.06%) 1	
Headache subjects affected / exposed occurrences (all)	51 / 241 (21.16%) 64	16 / 94 (17.02%) 19	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	86 / 241 (35.68%) 131	29 / 94 (30.85%) 35	
Febrile neutropenia subjects affected / exposed occurrences (all)	41 / 241 (17.01%) 47	19 / 94 (20.21%) 28	
Leukocytosis subjects affected / exposed occurrences (all)	14 / 241 (5.81%) 14	3 / 94 (3.19%) 3	
Leukopenia subjects affected / exposed occurrences (all)	13 / 241 (5.39%) 17	2 / 94 (2.13%) 2	
Neutropenia subjects affected / exposed occurrences (all)	48 / 241 (19.92%) 77	11 / 94 (11.70%) 11	

Thrombocytopenia subjects affected / exposed occurrences (all)	62 / 241 (25.73%) 84	20 / 94 (21.28%) 21	
Eye disorders Dry eye subjects affected / exposed occurrences (all)	13 / 241 (5.39%) 13	1 / 94 (1.06%) 1	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	11 / 241 (4.56%) 13	5 / 94 (5.32%) 5	
Abdominal pain subjects affected / exposed occurrences (all)	30 / 241 (12.45%) 33	15 / 94 (15.96%) 16	
Abdominal pain upper subjects affected / exposed occurrences (all)	18 / 241 (7.47%) 21	0 / 94 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	47 / 241 (19.50%) 54	22 / 94 (23.40%) 29	
Diarrhoea subjects affected / exposed occurrences (all)	68 / 241 (28.22%) 98	34 / 94 (36.17%) 42	
Dry mouth subjects affected / exposed occurrences (all)	13 / 241 (5.39%) 14	3 / 94 (3.19%) 3	
Dyspepsia subjects affected / exposed occurrences (all)	20 / 241 (8.30%) 20	6 / 94 (6.38%) 6	
Gingival bleeding subjects affected / exposed occurrences (all)	16 / 241 (6.64%) 16	3 / 94 (3.19%) 3	
Nausea subjects affected / exposed occurrences (all)	114 / 241 (47.30%) 164	39 / 94 (41.49%) 47	
Proctalgia			

subjects affected / exposed occurrences (all)	8 / 241 (3.32%) 9	5 / 94 (5.32%) 5	
Stomatitis subjects affected / exposed occurrences (all)	39 / 241 (16.18%) 39	18 / 94 (19.15%) 18	
Vomiting subjects affected / exposed occurrences (all)	80 / 241 (33.20%) 116	20 / 94 (21.28%) 25	
Skin and subcutaneous tissue disorders			
Petechiae subjects affected / exposed occurrences (all)	27 / 241 (11.20%) 31	6 / 94 (6.38%) 8	
Pruritus subjects affected / exposed occurrences (all)	15 / 241 (6.22%) 15	6 / 94 (6.38%) 8	
Rash subjects affected / exposed occurrences (all)	36 / 241 (14.94%) 41	9 / 94 (9.57%) 10	
Skin lesion subjects affected / exposed occurrences (all)	14 / 241 (5.81%) 14	1 / 94 (1.06%) 1	
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	15 / 241 (6.22%) 16	39 / 94 (41.49%) 3	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	20 / 241 (8.30%) 24	3 / 94 (3.19%) 3	
Back pain subjects affected / exposed occurrences (all)	26 / 241 (10.79%) 29	9 / 94 (9.57%) 9	
Muscle spasms subjects affected / exposed occurrences (all)	19 / 241 (7.88%) 22	0 / 94 (0.00%) 0	
Musculoskeletal pain			

subjects affected / exposed occurrences (all)	19 / 241 (7.88%) 20	6 / 94 (6.38%) 8	
Myalgia subjects affected / exposed occurrences (all)	15 / 241 (6.22%) 16	2 / 94 (2.13%) 2	
Pain in extremity subjects affected / exposed occurrences (all)	25 / 241 (10.37%) 26	6 / 94 (6.38%) 6	
Infections and infestations			
Bacteraemia subjects affected / exposed occurrences (all)	2 / 241 (0.83%) 2	5 / 94 (5.32%) 5	
Device related infection subjects affected / exposed occurrences (all)	9 / 241 (3.73%) 9	7 / 94 (7.45%) 7	
Enterococcal infection subjects affected / exposed occurrences (all)	1 / 241 (0.41%) 1	5 / 94 (5.32%) 5	
Pneumonia subjects affected / exposed occurrences (all)	11 / 241 (4.56%) 11	6 / 94 (6.38%) 6	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	17 / 241 (7.05%) 17	1 / 94 (1.06%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	18 / 241 (7.47%) 26	0 / 94 (0.00%) 0	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	48 / 241 (19.92%) 62	10 / 94 (10.64%) 10	
Hyperglycaemia subjects affected / exposed occurrences (all)	15 / 241 (6.22%) 17	7 / 94 (7.45%) 10	
Hypoalbuminaemia			

subjects affected / exposed	17 / 241 (7.05%)	7 / 94 (7.45%)
occurrences (all)	33	10
Hypocalcaemia		
subjects affected / exposed	27 / 241 (11.20%)	10 / 94 (10.64%)
occurrences (all)	36	10
Hypokalaemia		
subjects affected / exposed	76 / 241 (31.54%)	25 / 94 (26.60%)
occurrences (all)	124	45
Hypomagnesaemia		
subjects affected / exposed	36 / 241 (14.94%)	7 / 94 (7.45%)
occurrences (all)	56	12
Hyponatraemia		
subjects affected / exposed	21 / 241 (8.71%)	6 / 94 (6.38%)
occurrences (all)	36	6
Hypophosphataemia		
subjects affected / exposed	23 / 241 (9.54%)	10 / 94 (10.64%)
occurrences (all)	31	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 December 2013	The original protocol was amended prior to submission to the IND to incorporate the FDA's concurrence of the proposed dosing regimen. Protocol Amendment 1 was the first protocol disseminated to IRBs and investigators.
26 May 2015	<ul style="list-style-type: none"> - Increased in the study duration to 36 months. - Clarified that quizartinib should be taken in the morning. - Changed the dose escalation schedule. - Changed the schedule for assessment of response. - FLT3-ITD allelic ratio cut-off changed to $\geq 3\%$ from $> 3\%$. - Eligibility criteria clarified to state that subjects must be in first relapse or refractory (have not achieved a remission) to chemotherapy. Definition of duration of remission modified to allow the enrollment of subjects who relapsed 6 months after allogeneic transplant. - Bradycardia of less than 50 bpm added to the exclusion criteria. - Clarified the period to avoid pregnancy in the exclusion criteria. - The exclusion criterion of presence of a FLT3 D835 mutation at study enrollment was changed to exclude prior treatment with a FLT3 targeted therapy, including sorafenib or investigational FLT3 inhibitors. There were no changes in samples size due to this amendment. - Updated the packaging and storage information. - Added a table of P-glycoprotein inhibitors and inducers, - Added the requirement for a urine pregnancy test every 3 months during the treatment phase in women of child-bearing potential. - Specified that optional pharmacogenomic and pharmacoproteomic samples collected before dosing on Day 1 of Cycle 1 and at the end of treatment visit will be used for DNA, RNA, and PBMC isolation, in subjects who provided consent. - Clarified that an EOT case report form must be completed for subjects who discontinue quizartinib in order to proceed to HSCT. Clarified that for subjects receiving chemotherapy, the EOT visit is Day 29 of the last cycle. - Added an assessment of concomitant medications at the 30-Day Follow-up visit.
06 October 2015	<ul style="list-style-type: none"> - Changed the sponsor from Ambit Biosciences to DSI in all regions except Europe and to Daiichi Sankyo Development Limited in Europe. - Updated the total number of potential sites. - Clarified the following: age requirement, in inclusion criterion 2; that a local FLT3-ITD test may be used for enrollment after discussion with the Medical Monitor, if the central laboratory results are not available when the subject requires treatment initiation, in inclusion criterion 5; and that cases where subjects have been randomized and the FLT3-ITD local and central laboratory results were discordant, the subjects were permitted to continue quizartinib/salvage chemotherapy dosing. - Clarified that the sponsor will not have access to aggregate efficacy data, except when data from both treatment arms are combined. - Removed "Dispensing of quizartinib" and captured it as a footnote in the Schedules of Activities and Assessments. - Clarified expectations of when ECGs should occur. - Removed the detailed definition of the secondary efficacy endpoint. This information was included in statistical analysis plan. - Explained that Grade 3 or 4 QTcF prolongation events (average of triplicate ECG determinations by the central reading) should be reported within 24 hours.
19 November 2015	Updated exclusion criterion 9 to clarify that prior treatment with the multi-kinase inhibitor, midostaurin, was permitted.

04 May 2016	<ul style="list-style-type: none"> - Listed Daiichi Sankyo, Inc. as global sponsor due to organizational change in Europe. - Added information and clarified inclusion/exclusion criteria - Changed food and drug restrictions due to new data - Removed IB information - Updated the clinical exposure data - Added the following statement to the overall study design and plan, "the sponsor may allow subjects who did not receive quizartinib to crossover to the quizartinib monotherapy arm after database lock if the safety parameters in the eligibility criteria are met." - Corrected the day of the planned quizartinib dose increase from Cycle 2 Day 2 to Cycle 2 Day 1. - Added that Competent Authority officials may identify conditions warranting study termination or site closure - Clarified and harmonized drug description, packaging, storage conditions and accountability - Changed ECG and PK sample collection times based on new information - Clarified that subjects undergoing HSCT will be evaluated by phone for the 30-Day Follow-up and Long-Term Follow-up
15 August 2016	<ul style="list-style-type: none"> - Made all necessary changes to switch the study design from an adaptive design to a traditional group sequential design - Increased the planned number of subjects to 363 to reach 280 events in a reasonable time - Adjusted efficacy objectives and endpoints to measure duration of CR and CRc - Changed protocol text to ensure descriptions and analysis of efficacy and safety endpoints were consistent throughout the protocol and the SAP - Revised planned analyses for subjects who underwent HSCT and removed pharmacoeconomic analysis - Clarified definition and added guidance for withdrawal of consent and lost to follow-up - Corrected ANC and/or platelet counts to match the Cheson IWG Response criteria - Clarified reporting requirements for SAE of QTcF prolongation - Defined sub-groups to be analyzed for primary and secondary efficacy endpoints
30 June 2017	<ul style="list-style-type: none"> - Removed AC220 throughout as this refers to the salt form (quizartinib dihydrochloride) and not the freebase (quizartinib), and corrected to quizartinib throughout. - Updated the Sponsor address and information for the DSI Medical Monitor. - Added a statement that the tasks performed by the SAC and the DMC during the interim analysis will be documented in the Interim Analysis Plan. - Added that safety data will be summarized by pre-defined sub-groups. - Clarified the definition and classification criteria for "No Response" subjects. - Provided a summary of findings from the Phase 1 Study of quizartinib following HSCT (Study 2689-CL-0011). - Added specific screening procedures, inclusion and exclusion criteria and schedule of activities and assessments for subjects crossing over from salvage chemotherapy to quizartinib. - Changed the site of peripheral blood screenings for FLT3-ITD testing from "Genoptix" to "Navigate BioPharma Services, Inc." - Changed the frequency of urine pregnancy tests from monthly to every 3 months in subjects receiving quizartinib after HSCT - Added instructional language for subjects who discontinue salvage chemotherapy and do not qualify for cross-over - Added a description of the methodology for the Navigate FLT3-ITD mutation assay

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported