

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	v1	
This version publication date	22 March 2019	
First version publication date	22 March 2019	
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,
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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?	No	
Global end of trial reached?	No	

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	31 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Popul	lation	of	trial	sub	jects
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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	

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	

EU-CTR publication date: 22 March 2019

Subject disposition

Recruitment

Recruitment details:

Of 563 patients assessed for eligibility, 367 were randomized and 335 received treatment

Pre-assignment

Screening details:

The study was conducted at 48 sites in Europe, 30 sites in North America, 11 sites in Asia, and 5 sites in Australia. The number of subjects enrolled in each region follows: Europe and Australia (195 patients), North America (141 patients), and Asia (31 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 monotherapy	
Arm description:		
Patients received monotherapy with quiz	artinib dihydrochloride	
Arm type	Experimental	
Investigational medicinal product name	Quizartinib	
Investigational medicinal product code		
Other name	AC010220 x 2HCl	
Pharmaceutical forms	Tablet	
Routes of administration	Oral use	
Dosage and administration details:		
Tablet; 30 mg and 20 mg, Oral tablets for	or daily administration	
Arm title	Salvage chemotherapy	
Arm description:		
Patients received standard of care salvagintravenously [MEC and FLAG-IDA]),	ge chemotherapy (administered subcutaneously [LoDac] or	
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 monotherapy	Salvage chemotherapy
Started	245	122
Received treatment (safety analysis set)	241	94 [1]
Died	88 [2]	84 [3]
Withdrew consent	7 [4]	22 [5]
Dropped out with no reason specified	2 [6]	0 [7]
Lost to follow-up	3 [8]	0 [9]
Completed	200	106
Not completed	45	16
Still on Study	45	16

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These are interim results, laid out this way to show the patients who have not completed the trial as those who are continuing.

Baseline characteristics

Reporting groups		
Reporting group title Quizartinib monotherapy		
Reporting group description:		
Patients received monotherapy with quizartinib dihydrochloride		
Reporting group title	Salvage chemotherapy	
Reporting group description:		

Patients received standard of care salvage chemotherapy (administered subcutaneously [LoDac] or intravenously [MEC and FLAG-IDA]),

Reporting group values	Quizartinib monotherapy	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

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End point values	Quizartinib monotherapy	Salvage chemotherapy	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	245 ^[4]	122 ^[5]	
Units: weeks			
median (inter-quartile range (Q1-Q3))	27.0 (15.4 to 62.6)	20.4 (8.3 to 39.6)	

- [4] Intent to treat analysis set
- [5] Intent to treat analysis set

Statistical analyses

Statistical analysis title	Hazard Ratio (Relative to Salvage Chemotherapy)
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Statistical analysis description:

Stratified analysis - stratification factors include prior therapy and response (Relapsed in \leq 6 months (not post-HSCT), Refractory, or relapsed in \leq 6

months post allogeneic HSCT), and pre-selected chemotherapy (High intensity chemotherapy [MEC or FLAG-IDA], or low intensity chemotherapy [LoDAC])

Comparison groups	Quizartinib monotherapy v Salvage chemotherapy
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	other ^[6]
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

Notes:

[6] - Interim analysis of the primary measure at the data cut off point in February 2018

Secondary: Event-Free Survival

End point title	Event-Free Survival

End point description:

Time (weeks) from randomization until documented refractory disease, relapse after complete composite remission (CRc), or death from any cause, whichever is observed first

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End point timeframe:

at the end of the trial (approximately 5 years, 2 months)

End point values	Quizartinib monotherapy	Salvage chemotherapy	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	0 ^[7]	0[8]	
Units: weeks			
geometric mean (standard deviation)	()	()	

- [7] The time point has not been reached for analysis of this endpoint.
- [8] The time point has not been reached for analysis of this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free survival at Data Cut-off

End point title	Event-free survival at Data Cut-off

End point description:

Event-free survival 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
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End point timeframe:

At data cut off in February 2018 (approximately 3 years, 9 months)

End point values	Quizartinib monotherapy	Salvage chemotherapy	
Subject group type	Reporting group	Reporting group	
Number of subjects analysed	245 ^[9]	122 ^[10]	
Units: weeks			
median (inter-quartile range (Q1-Q3))	6.0 (0.1 to 19.7)	3.7 (0.1 to 17.0)	

Notes:

[9] - Intent to treat analysis set

[10] - Intent to treat analysis set

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 monotherapy v Salvage chemotherapy
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	other ^[11]
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	

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Notes:

[11] - Interim analysis of the secondary measure at the data cut off point in February 2018

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), by the date of data cut-off, which was 22 Feb 2018.

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. Consequently, the frequency of most TEAE categories is greater in the quizartinib arm.

most TEAE categories is greater in the c	uizartinib arm.
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Quizartinib monotherapy
Reporting group description:	
Patients receiving quizartinib monothera	пру
Reporting group title	Salvage chemotherapy
Reporting group description:	
Patients receiving standard of care	

Serious adverse events	Quizartinib monotherapy	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			

	1	1	
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	
nmune system disorders	1	Ī	

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	İ		
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	

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		1	
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	l i		

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 offseted / synesod	l		1
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	ĺ		
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	(/ 244 / 2 / 220)	0 / 0 / (0 000)	
	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	İ		
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	İ		
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	
1		0,0	
Pancytopenia subjects affected / exposed	2 / 2/1 /1 2/0/\	0 / 04 (0 000/)	
occurrences causally related to	3 / 241 (1.24%)	0 / 94 (0.00%) 0 / 0	
treatment / all deaths causally related to treatment / all	0 / 0	0 / 0	
1	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	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		ĺ
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		Ī
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	l	1

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			l I

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	
		:	

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%) 0 / 0	1			
treatment / all deaths causally related to treatment / all		1 / 241 (0.41%)	0 / 94 (0.00%)	
treatment / all		0 / 1	0 / 0	
Subjects affected / exposed		0 / 0	0 / 0	
occurrences causally related to treatment / all 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 / 0 Escherichia sepsis subjects affected / exposed 0 / 241 (0.83%) 3 / 94 (3.19%) occurrences 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 / 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 0 / 0 Gastroenteritis subjects affected / exposed 3 / 241 (1.24%) 0 / 94 (0.00%) occurrences causally related to treatment / all 0 / 0 0 / 0 Gastroenteritis subjects affected / exposed 0 / 3 0 / 0 Gastroenteritis rotavirus subjects affected / exposed 1 / 241 (0.41%) 0 / 94 (0.00%) occurrences 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 / 0 0 / 0	Enterocolitis infectious			
treatment / all deaths causally related to treatment / all Escherichia bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Escherichia sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all fungal skin infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
treatment / all		1 / 1	0 / 0	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to		0 / 0	0 / 0	
occurrences causally related to treatment / all deaths causally related to	Escherichia bacteraemia			
treatment / all deaths causally related to treatment / all Escherichia sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Fungal skin infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to	subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
Escherichia sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to		0 / 0	0 / 1	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Fungal skin infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to		0 / 0	0 / 0	
occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Escherichia sepsis			
treatment / all deaths causally related to treatment / all Pungal skin infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to	subjects affected / exposed	2 / 241 (0.83%)	3 / 94 (3.19%)	
treatment / all		0 / 2	2/3	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to		0 / 0	0 / 0	
occurrences causally related to treatment / all deaths causally related to treatment / all	Fungal skin infection			
treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all deaths causally related to	subjects affected / exposed	0 / 241 (0.00%)	1 / 94 (1.06%)	
treatment / all		0 / 0	1 / 1	
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to		0 / 0	0 / 0	
occurrences causally related to treatment / all deaths causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to	Gastroenteritis			
treatment / all deaths causally related to treatment / all Gastroenteritis rotavirus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to deaths causally related to	subjects affected / exposed	3 / 241 (1.24%)	0 / 94 (0.00%)	
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 deaths causally related to		0 / 3	0 / 0	
subjects affected / exposed $1/241 (0.41\%) = 0/94 (0.00\%)$ occurrences causally related to treatment / all deaths causally related to		0 / 0	0 / 0	
occurrences causally related to treatment / all deaths causally related to	Gastroenteritis rotavirus			
treatment / all deaths causally related to	subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
		0 / 1	0 / 0	
		0 / 0	0 / 0	
Hepatitis A	Hepatitis A	ĺ		
subjects affected / exposed 1 / 241 (0.41%) 0 / 94 (0.00%)	subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all 0 / 1 0 / 0		0 / 1	0 / 0	
deaths causally related to treatment / all 0 / 0 0 / 0		0/0	0 / 0	
Infection	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]		ļ
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	l		İ

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	j	· 	·
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	l i		

	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			
İ	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			
j	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			
İ	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			
İ	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	Ì		
	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	
j	Urinary tract infection	i İ		j
	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	
j	Urinary tract infection bacterial	j		j
•				ı

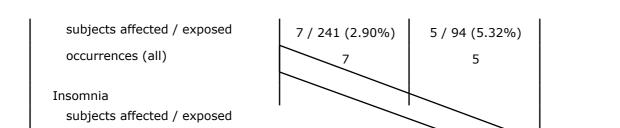
	_	_	_
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	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		I	I
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 monotherapy	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			

occurrences (all) 21 8 Pyrexia subjects affected / exposed occurrences (all) 88 / 241 (36.51%) 42 / 94 (44.68%) Immune system disorders Graft versus host disease subjects affected / exposed occurrences (all) 14 / 241 (5.81%) 0 / 94 (0.00%) Graft versus host disease in skin subjects affected / exposed occurrences (all) 16 / 241 (6.64%) 0 / 94 (0.00%) Respiratory, thoracic and mediastinal disorders 16 / 241 (23.24%) 13 / 94 (13.83%) Cough subjects affected / exposed occurrences (all) 56 / 241 (23.24%) 13 / 94 (13.83%) Dyspnoea subjects affected / exposed occurrences (all) 48 / 241 (19.92%) 8 / 94 (8.51%) Occurrences (all) 34 9 Nasal congestion subjects affected / exposed occurrences (all) 9 / 241 (3.73%) 5 / 94 (5.32%) Oropharyngeal pain subjects affected / exposed occurrences (all) 25 / 241 (10.37%) 6 / 94 (6.38%) OPleural effusion subjects affected / exposed occurrences (all) 26 7 7 Pleural effusion subjects affected / exposed occurrences (all) 14 / 241 (5.81%) 2 / 94 (2.13%) Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) 19 / 241 (7.88%) 4 / 94 (4.26%)	subjects affected / exposed	19 / 241 (7.88%)	8 / 94 (8.51%)	
subjects affected / exposed occurrences (all) Immune system disorders Graft versus host disease subjects affected / exposed occurrences (all) Graft versus host disease in skin subjects affected / exposed occurrences (all) Graft versus host disease in skin subjects affected / exposed occurrences (all) Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) As y 4 (8.51%) OCCURRENCE (all) As y 4 (8.51%) OCCURRENCE (all) Pospharyngeal pain subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pileural effusion subjects affected / exposed occurrences (all) Pileural effusion subjects affected / exposed occurrences (all) Peychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) At / 94 (4.4.6%) 42 / 94 (4.4.68%) O/ 94 (0.00%) O/ 94 (0.00%) O/ 94 (0.00%) O/ 94 (0.00%) O/ 94 (0.00%) O/ 94 (1.3.83%) O/ 94 (1.3.83%) O/ 94 (1.3.83%) O/ 94 (1.3.83%) O/ 94 (1.3.83%) O/ 94 (8.51%) O/ 94 (8.51%) O/ 94 (5.32%) O/ 94 (5.32%) O/ 94 (5.32%) O/ 94 (5.32%) O/ 94 (5.32%) O/ 94 (5.32%) O/ 94 (6.38%) O/ 94 (occurrences (all)	21	8	
Description 130 69 130 69 130 69 130 69 130 69 130 69 130 69 130 69 130 69 130 69 130 69 14 241 (5.81%) 0 / 94 (0.00%) 0 /	Pyrexia			
Immune system disorders Graft versus host disease subjects affected / exposed occurrences (all) 14 0 0 0 0 0 0 0 0 0	1	88 / 241 (36.51%)	42 / 94 (44.68%)	
Graft versus host disease subjects affected / exposed occurrences (all) Graft versus host disease in skin subjects affected / exposed occurrences (all) Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 14 / 241 (5.81%) 0 / 94 (0.00%) 0 / 94 (0.	occurrences (all)	130	69	
subjects affected / exposed occurrences (all) Graft versus host disease in skin subjects affected / exposed occurrences (all) Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Popharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 14 / 241 (5.81%) 19 / 241 (0.00%) 0 / 94	1			
occurrences (all) Graft versus host disease in skin subjects affected / exposed occurrences (all) Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) ANASI congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Peychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 14 / 94 (4.26%)		14 (244 (5 249 ()	0 / 0 / / 0 000/)	
Graft versus host disease in skin subjects affected / exposed occurrences (all) Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pieural effusion subjects affected / exposed occurrences (all) Peychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 16 / 241 (6.64%) 13 / 94 (13.83%) 13 / 94 (13.83%) 13 / 94 (13.83%) 8 / 94 (8.51%) 8 / 94 (8.51%) 9 5 / 94 (5.32%) 5 / 94 (5.32%) 6 / 94 (6.38%) 2 / 94 (2.13%) 2 / 94 (2.13%) 2 / 94 (2.13%) 9 Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)				
subjects affected / exposed occurrences (all) Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) 16 / 241 (23.24%) 13 / 94 (13.83%) 14 / 94 (8.51%) 13 / 94 (13.83%) 13 / 94 (13.83%) 14 / 94 (13.83%) 15 / 94 (13.83%) 1	occurrences (all)	14	0	
Respiratory, thoracic and mediastinal disorders	Graft versus host disease in skin			
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed	subjects affected / exposed	16 / 241 (6.64%)	0 / 94 (0.00%)	
disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 13 / 94 (13.83%) 14 / 94 (8.51%) 16 / 94 (8.51%) 17 / 94 (5.32%) 18 / 94 (8.51%) 19 / 241 (10.37%) 19 / 94 (6.38%) 20 / 94 (6.38%) 20 / 94 (2.13%) 21 / 94 (2.13%) 22 / 94 (2.13%) 23 / 94 (2.13%) 24 / 94 (4.26%)	occurrences (all)	18	0	
disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 13 / 94 (13.83%) 14 / 94 (8.51%) 16 / 94 (8.51%) 17 / 94 (5.32%) 18 / 94 (8.51%) 19 / 241 (10.37%) 19 / 94 (6.38%) 20 / 94 (6.38%) 20 / 94 (2.13%) 21 / 94 (2.13%) 22 / 94 (2.13%) 23 / 94 (2.13%) 24 / 94 (4.26%)	Respiratory, thoracic and mediastinal			
subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) 13 / 94 (13.83%) 14 / 241 (19.92%) 8 / 94 (8.51%) 8 / 94 (8.51%) 9 5 / 94 (5.32%) 6 / 94 (6.38%) 2 / 94 (6.38%) 2 / 94 (2.13%) 2 / 94 (2.13%) 2 / 94 (2.13%) 4 / 94 (4.26%)	disorders			
Occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) 14 / 241 (5.81%) 2 / 94 (2.13%) occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	_	56 / 244 /22 249/	12 / 04 /12 020/)	
Dyspnoea subjects affected / exposed occurrences (all) 61 11 Epistaxis subjects affected / exposed 28 / 241 (11.62%) 8 / 94 (8.51%) occurrences (all) 34 9 Nasal congestion subjects affected / exposed 9 / 241 (3.73%) 5 / 94 (5.32%) occurrences (all) 9 5 Oropharyngeal pain subjects affected / exposed 25 / 241 (10.37%) 6 / 94 (6.38%) occurrences (all) 26 7 Pleural effusion subjects affected / exposed occurrences (all) 14 / 241 (5.81%) 2 / 94 (2.13%) occurrences (all) 2 / 94 (2.13%) occurrences (all) 14 2				
subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) Al / 94 (8.51%) 8 / 94 (8.51%) 9 / 241 (3.73%) 5 / 94 (5.32%) 6 / 94 (6.38%) 2 / 94 (2.13%) 2 / 94 (2.13%) 4 / 94 (4.26%)	occurrences (all)	64	14	
occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	Dyspnoea			
Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	subjects affected / exposed	48 / 241 (19.92%)	8 / 94 (8.51%)	
subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed occurrenced (all) Psychiatric disorders Anxiety subjects affected / exposed occurrenced (all) 28 / 241 (11.62%) 8 / 94 (8.51%) 9 8 / 94 (8.51%) 9 5 / 94 (5.32%) 6 / 94 (6.38%) 6 / 94 (6.38%) 7 25 / 241 (10.37%) 6 / 94 (6.38%) 7 2 / 94 (2.13%) 2 / 94 (2.13%) 6 / 94 (6.38%) 7 / 94 (6.38%	occurrences (all)	61	11	
Occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 9 / 241 (3.73%) 5 / 94 (5.32%) 5 / 94 (5.32%) 6 / 94 (6.38%) 6 / 94 (6.38%) 7 2 / 94 (2.13%) 2 / 94 (2.13%) 4 / 94 (4.26%)	Epistaxis			
Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 9 / 241 (3.73%) 5 / 94 (5.32%) 5 / 94 (5.32%) 6 / 94 (6.38%) 7 2 / 94 (2.13%) 2 / 94 (2.13%) 2 / 94 (2.13%) 4 / 94 (4.26%)	subjects affected / exposed	28 / 241 (11.62%)	8 / 94 (8.51%)	
subjects affected / exposed 9 / 241 (3.73%) 5 / 94 (5.32%) occurrences (all) 9 5 Oropharyngeal pain subjects affected / exposed occurrences (all) 25 / 241 (10.37%) 6 / 94 (6.38%) occurrences (all) 26 7 Pleural effusion subjects affected / exposed occurrences (all) 14 / 241 (5.81%) 2 / 94 (2.13%) occurrences (all) 14 2 Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	occurrences (all)	34	9	
subjects affected / exposed 9 / 241 (3.73%) 5 / 94 (5.32%) occurrences (all) 9 5 Oropharyngeal pain subjects affected / exposed occurrences (all) 25 / 241 (10.37%) 6 / 94 (6.38%) occurrences (all) 26 7 Pleural effusion subjects affected / exposed occurrences (all) 14 / 241 (5.81%) 2 / 94 (2.13%) occurrences (all) 14 2 Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	Nasal congestion			
Occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 5 6 / 94 (6.38%) 6 / 94 (6.38%) 2 / 94 (2.13%) 2 / 94 (2.13%) 2 / 94 (2.13%) 2 / 94 (2.13%) 4 / 94 (4.26%)	_	9 / 241 (3.73%)	5 / 94 (5.32%)	
Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) 14 / 241 (5.81%) occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	occurrences (all)		,	
subjects affected / exposed			, , ,	
occurrences (all) 26 7 Pleural effusion subjects affected / exposed occurrences (all) 14 / 241 (5.81%) 14 2 Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)				
Pleural effusion subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 14 / 241 (5.81%) 2 / 94 (2.13%) 2 Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)		25 / 241 (10.37%)	6 / 94 (6.38%)	
subjects affected / exposed occurrences (all) Psychiatric disorders Anxiety subjects affected / exposed 14 / 241 (5.81%) 2 / 94 (2.13%) 2 Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	occurrences (all)	26	7	
occurrences (all) 14 2 Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	Pleural effusion			
Psychiatric disorders Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	subjects affected / exposed	14 / 241 (5.81%)	2 / 94 (2.13%)	
Anxiety subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	occurrences (all)	14	2	
subjects affected / exposed 19 / 241 (7.88%) 4 / 94 (4.26%)	Psychiatric disorders			
13 / 2 / 2 (/100 / 0) 1 / 3 / (/120 / 0)	1			
occurrences (all) 21 4	subjects affected / exposed	19 / 241 (7.88%)	4 / 94 (4.26%)	
	occurrences (all)	21	4	
Confusional state	Confusional state			



subjects affected / exposed	35 / 241 (14.52%)	14 / 94 (14.89%)	
occurrences (all)	45	17	
Injury, poisoning and procedural complications Contusion			
subjects affected / exposed	15 / 241 (6.22%)	2 / 94 (2.13%)	
occurrences (all)	17	2	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	8 / 241 (3.32%)	5 / 94 (5.32%)	
occurrences (all)			
occurrences (aii)	8	5	
Nervous system disorders Dizziness			
subjects affected / exposed	36 / 241 (14.94%)	10 / 94 (10.64%)	
occurrences (all)	41		
occurrences (un)	41	10	
Dysgeusia			
subjects affected / exposed	22 / 241 (9.13%)	1 / 94 (1.06%)	
occurrences (all)	22	1	
 Headache			
subjects affected / exposed	51 / 241 (21.16%)	16 / 94 (17.02%)	
occurrences (all)	64	19	
, ,	04	19	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	86 / 241 (35.68%)	29 / 94 (30.85%)	
occurrences (all)	131	35	
Febrile neutropenia			
subjects affected / exposed	41 / 241 (17.01%)	19 / 94 (20.21%)	
occurrences (all)	47	28	
, ,	1,	20	
Leukocytosis			
subjects affected / exposed	14 / 241 (5.81%)	3 / 94 (3.19%)	
occurrences (all)	14	3	
Leukopenia			
subjects affected / exposed	13 / 241 (5.39%)	2 / 94 (2.13%)	
occurrences (all)			
Coourt energy (un)	17	2	
Neutropenia			
subjects affected / exposed	48 / 241 (19.92%)	11 / 94 (11.70%)	
occurrences (all)	77	11	

Thrombocytopenia subjects affected / exposed	62 / 241 (25.73%)	20 / 94 (21.28%)
occurrences (all)	84	20 / 94 (21.26%)
Eye disorders		
Dry eye		
subjects affected / exposed	13 / 241 (5.39%)	1 / 94 (1.06%)
occurrences (all)	13	1
Gastrointestinal disorders		
Abdominal distension		
subjects affected / exposed	11 / 241 (4.56%)	5 / 94 (5.32%)
occurrences (all)	13	5
Abdominal pain		
subjects affected / exposed	30 / 241 (12.45%)	15 / 94 (15.96%)
occurrences (all)	33	16
Abdominal pain upper		
subjects affected / exposed	18 / 241 (7.47%)	0 / 94 (0.00%)
occurrences (all)	'	
occurrences (an)	21	0
Constipation		
subjects affected / exposed	47 / 241 (19.50%)	22 / 94 (23.40%)
occurrences (all)	54	29
Diarrhoea		
subjects affected / exposed	68 / 241 (28.22%)	34 / 94 (36.17%)
occurrences (all)	98	42
,	30	72
Dry mouth		
subjects affected / exposed	13 / 241 (5.39%)	3 / 94 (3.19%)
occurrences (all)	14	3
Dyspepsia		
subjects affected / exposed	20 / 241 (8.30%)	6 / 94 (6.38%)
occurrences (all)	20	6
Gingival bleeding		
subjects affected / exposed	16 / 241 (6.64%)	3 / 94 (3.19%)
occurrences (all)	16	3
Nauroa		
Nausea subjects affected / exposed	114 / 241 /47 200/	20 / 04 /41 400/ \
	114 / 241 (47.30%)	
occurrences (all)	164	47
Proctalgia		

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

subjects affected / exposed	19 / 241 (7.88%)	6 / 94 (6.38%)	
occurrences (all)	20	8	
Market			
Myalgia subjects affected / exposed	15 / 241 (6.22%)	2 / 94 (2.13%)	
occurrences (all)	16		
occurrences (un)	16	2	
Pain in extremity			
subjects affected / exposed	25 / 241 (10.37%)	6 / 94 (6.38%)	
occurrences (all)	26	6	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	2 / 241 (0.83%)	5 / 94 (5.32%)	
occurrences (all)	2	5	
Device related infection			
subjects affected / exposed	9 / 241 (3.73%)	7 / 94 (7.45%)	
occurrences (all)	9	7	
Enterococcal infection subjects affected / exposed	1 / 241 / 2 410/)	5 / 0 / (5 220/)	
	1 / 241 (0.41%)	5 / 94 (5.32%)	
occurrences (all)	1	5	
Pneumonia			
subjects affected / exposed	11 / 241 (4.56%)	6 / 94 (6.38%)	
occurrences (all)	11	6	
Upper respiratory tract infection			
subjects affected / exposed	17 / 241 (7.05%)	1 / 94 (1.06%)	
occurrences (all)	17	1	
	1,	1	
Urinary tract infection			
subjects affected / exposed	18 / 241 (7.47%)	0 / 94 (0.00%)	
occurrences (all)	26	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	48 / 241 (19.92%)	10 / 94 (10.64%)	
occurrences (all)	62	10	
 Hyperglycaemia			
subjects affected / exposed	15 / 241 (6.22%)	7 / 94 (7.45%)	
occurrences (all)	17	10	
Hypoalbuminaemia			

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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	- 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 ≥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	- 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

- 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

- 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

- 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

EU-CTR publication date: 22 March 2019