Clinical trial results:
A Phase 2, Randomized, Open-Label Study of the Safety and Efficacy of Two Doses of Quizartinib (AC220; ASP2689) in Subjects with FLT3-ITD Positive Relapsed or Refractory Acute Myeloid Leukemia (AML)

Summary

EudraCT number	2011-005408-13
Trial protocol	GB IT
Global end of trial date	09 March 2015

Results information

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

Trial information

Trial identification

Sponsor protocol code	2689-CL-2004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01565668
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Study Director, Daiichi Sankyo, Inc., 1 908-992-6400,
Scientific contact	Study Director, Daiichi Sankyo, Inc., 1 908-992-6400,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives are to evaluate the rate of Grade 2 or higher QTcF prolongation and to evaluate the composite complete remission rate (CRc), defined as the confirmed rate of complete remission (CR) plus complete remission with incomplete platelet recovery (CRp) or incomplete hematological recovery (CRi) at different doses of AC220.

Protection of trial subjects:

This trial 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	02 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 58
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	76
EEA total number of subjects	18

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)	56

From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 70 subjects were to be randomized equally between 2 treatment arms of quizartinib (at approximately 50 centers in North America and Europe), to receive daily doses of 30 mg or 60 mg. This was to provide, at the minimum, 32 centrally tested FLT3-ITD (+) AML subjects.

Pre-assignment

Screening details:

Of the subjects screened, 76 were enrolled into the intention to treat (ITT) analysis set. Two patients who were randomized to quizartinib (60 mg/day) did not receive study drug, so are not included in the data.

Pre-assignment period milestones

Number of subjects started	76
Number of subjects completed	76

Period 1

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

Blinding implementation details:

Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 30 mg

Arm description:

Patients were randomized to receive 30 mg quizartinib once daily

Arm type	Experimental
Investigational medicinal product name	Quizartinib
Investigational medicinal product code	
Other name	AC220, ASP2689
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Once-daily dose of oral solution for continuous 28-day cycles until deemed no longer beneficial by investigator

Arm title	Cohort 2 60 mg

Arm description:

Patients were randomized to receive 60 mg quizartinib once daily

Arm type	Experimental
Investigational medicinal product name	Quizartinib
Investigational medicinal product code	
Other name	AC220, ASP2689
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Once-daily dose of oral solution for continuous 28-day cycles until deemed no longer beneficial by investigator

Number of subjects in period 1	Cohort 1 30 mg	Cohort 2 60 mg
Started	38	38
Started treatment	38	38
Completed treatment per protocol	0	0
Started 30-day follow-up	37	37
Completed 30-day follow-up	11	5
Started long-term follow-up	36	33
Completed long-term follow-up	0	0
Completed	0	0
Not completed	38	38
Consent withdrawn by subject	1	3
HSCT Transplant	11	15
Adverse event, non-fatal	6	1
Death	2	1
Progressive Disease	13	14
Patient went on Hospice Care	1	-
Randomized But Never Received Study Drug	-	2
Lack of efficacy	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	76	76	
Age categorical Units: Subjects			
Adults (18-64 years)	56	56	
From 65-84 years	20	20	
Age continuous Units: years			
median	54.5		
full range (min-max)	19 to 77	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	44	44	

End points

End points reporting groups

Reporting group title	Cohort 1 30 mg
Reporting group description:	
Patients were randomized to receive 30 mg quizartinib once daily	
Reporting group title	Cohort 2 60 mg
Reporting group description:	
Patients were randomized to receive 60 mg quizartinib once daily	

Primary: Number of Subjects Who Achieved Composite Complete Remission (CRc)

End point title	Number of Subjects Who Achieved Composite Complete Remission (CRc)[1]
End point description:	
CRc is defined as Complete remission (CR) + Complete remission with incomplete platelet recovery (CRp) + Complete remission with incomplete hematological recovery (CRi)	
End point type	Primary
End point timeframe:	
After two 28-day cycles	

Notes:

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

End point values	Cohort 1 30 mg	Cohort 2 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: Patients	18	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Achieved Complete Remission (CR)

End point title	Number of Subjects Who Achieved Complete Remission (CR)
End point description:	
Patient must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state (< 5% bone marrow blasts in bone marrow, no blasts with Auer rods and no persistence of extramedullary disease) and must have an absolute neutrophil count (ANC) ≥ 1x109/L and platelet count ≥ 100 x 109/L and they will be red blood cell (RBC) and platelet transfusion independent (defined as 4 weeks without RBC transfusions and 1 week without platelet transfusion).	
End point type	Secondary
End point timeframe:	
After two complete 28-day cycles	

End point values	Cohort 1 30 mg	Cohort 2 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: Patients	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response In Subjects Who Achieved CRc or PR

End point title	Duration of Response In Subjects Who Achieved CRc or PR

End point description:

Duration of response (DOR) was defined as the time from either the first CRc or PR until the date of relapse (any type) for subjects who achieved CRc or PR (relapse date - first CRc or PR disease assessment date + 1). DOR was measured in weeks and categorized by quartiles; the 50% quartile is presented.

End point type	Secondary

End point timeframe:

Time from first CRc or PR until date of relapse

End point values	Cohort 1 30 mg	Cohort 2 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	27		
Units: Weeks				
number (confidence interval 95%)				
DOR; 50% quartile	7.3 (4.1 to 11.9)	9.1 (5.6 to 21.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CRc in Subjects Who Achieved CRc

End point title	Time to CRc in Subjects Who Achieved CRc

End point description:

Time to CRc was defined as the time from the date of randomization until the first disease assessment of CRc (first CRc disease assessment date - randomization date +1). Time to CRc was only assessed who achieved CRc. Time to CRc was measured in weeks and categorized by quartiles; the 50% quartile is presented.

End point type	Secondary

End point timeframe:

Time from the date of randomization until the first disease assessment of CRc

End point values	Cohort 1 30 mg	Cohort 2 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: weeks				
number (confidence interval 95%)				
Time to CRc; 50% quartile	4.4 (4.1 to 7.7)	4.6 (4.1 to 8.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Maximum QTcF Value in Subjects Who Received Quizartinib

End point title	Maximum QTcF Value in Subjects Who Received Quizartinib

End point description:

The number of patients with maximum corrected for heart rate using Fridericia's factor (QTcF) value (msec) on study is presented. Grade 2 or higher prolongation is defined as QTcF >480 msec.

End point type	Other pre-specified

End point timeframe:

After 2 continuous 28-day cycles

End point values	Cohort 1 30 mg	Cohort 2 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	36		
Units: Subjects				
number (not applicable)				
<450	18	13		
≥450 and ≤480	16	17		
>480 and ≤500	2	5		
>500	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the trial for adverse events, plus 30 days for serious AEs

Adverse event reporting additional description:

Of note, AML disease progression (including the MedDRA verbatim terms of AML progression and disease progression, malignant neoplasm progression, and leukocytosis) is reported as an AE in the data output and in the in-text tables; however, it is not considered an AE because of the patient population under study and is not further discussed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Cohort 1 30 mg
Reporting group description: -	
Reporting group title	Cohort 2 60 mg

Reporting group description: -

Serious adverse events	Cohort 1 30 mg	Cohort 2 60 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 38 (65.79%)	25 / 36 (69.44%)	
number of deaths (all causes)	9	13	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	5 / 38 (13.16%)	7 / 36 (19.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 5	0 / 6	
Lung neoplasm			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Non-cardiac chest pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	3 / 38 (7.89%)	5 / 36 (13.89%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (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	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	
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	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ventricular tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	7 / 38 (18.42%)	6 / 36 (16.67%)	
occurrences causally related to treatment / all	3 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caecitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (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	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (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	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess intestinal			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis fungal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candidiasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			

subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile sepsis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device related infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			

subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 38 (7.89%)	6 / 36 (16.67%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia fungal			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			

subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis aspergillus			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (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	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			

subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (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			
Dehydration			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1 30 mg	Cohort 2 60 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 38 (97.37%)	36 / 36 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Hypotension			
subjects affected / exposed	5 / 38 (13.16%)	4 / 36 (11.11%)	
occurrences (all)	5	4	
Thrombophlebitis superficial			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	3 / 38 (7.89%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Catheter site erythema			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Catheter site pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Chest discomfort			
subjects affected / exposed	3 / 38 (7.89%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Chills			
subjects affected / exposed	5 / 38 (13.16%)	3 / 36 (8.33%)	
occurrences (all)	5	3	
Fatigue			
subjects affected / exposed	13 / 38 (34.21%)	8 / 36 (22.22%)	
occurrences (all)	13	8	
Malaise			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Mucosal inflammation			
subjects affected / exposed	6 / 38 (15.79%)	5 / 36 (13.89%)	
occurrences (all)	6	5	
Non-cardiac chest pain			
subjects affected / exposed	0 / 38 (0.00%)	4 / 36 (11.11%)	
occurrences (all)	0	4	
Oedema			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Oedema peripheral			
subjects affected / exposed	8 / 38 (21.05%)	6 / 36 (16.67%)	
occurrences (all)	8	6	
Pain			
subjects affected / exposed	2 / 38 (5.26%)	4 / 36 (11.11%)	
occurrences (all)	2	4	

Pyrexia			
subjects affected / exposed	10 / 38 (26.32%)	10 / 36 (27.78%)	
occurrences (all)	10	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 38 (21.05%)	9 / 36 (25.00%)	
occurrences (all)	8	9	
Dyspnoea			
subjects affected / exposed	8 / 38 (21.05%)	5 / 36 (13.89%)	
occurrences (all)	8	5	
Dyspnoea exertional			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	6 / 38 (15.79%)	4 / 36 (11.11%)	
occurrences (all)	6	4	
Nasal congestion			
subjects affected / exposed	2 / 38 (5.26%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Oropharyngeal pain			
subjects affected / exposed	5 / 38 (13.16%)	6 / 36 (16.67%)	
occurrences (all)	5	6	
Pleural effusion			
subjects affected / exposed	2 / 38 (5.26%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Productive cough			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Rhinorrhoea			
subjects affected / exposed	3 / 38 (7.89%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Sinus congestion			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 38 (2.63%)	5 / 36 (13.89%)	
occurrences (all)	1	5	
Confusional state			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Insomnia			
subjects affected / exposed	2 / 38 (5.26%)	5 / 36 (13.89%)	
occurrences (all)	2	5	
Hallucination, visual			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 38 (7.89%)	3 / 36 (8.33%)	
occurrences (all)	3	3	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 38 (5.26%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Blood bilirubin increased			
subjects affected / exposed	3 / 38 (7.89%)	3 / 36 (8.33%)	
occurrences (all)	3	3	
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 38 (5.26%)	5 / 36 (13.89%)	
occurrences (all)	2	5	
Platelet count decreased			
subjects affected / exposed	3 / 38 (7.89%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
White blood cell count decreased			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	3 / 38 (7.89%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Fall			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Procedural pain			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Transfusion reaction			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Tachycardia			
subjects affected / exposed	3 / 38 (7.89%)	6 / 36 (16.67%)	
occurrences (all)	3	6	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	3 / 38 (7.89%)	4 / 36 (11.11%)	
occurrences (all)	3	4	
Dysgeusia			
subjects affected / exposed	6 / 38 (15.79%)	2 / 36 (5.56%)	
occurrences (all)	6	2	
Headache			
subjects affected / exposed	4 / 38 (10.53%)	9 / 36 (25.00%)	
occurrences (all)	4	9	
Paraesthesia			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Tremor			

subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 38 (44.74%)	9 / 36 (25.00%)	
occurrences (all)	17	9	
Febrile neutropenia			
subjects affected / exposed	5 / 38 (13.16%)	7 / 36 (19.44%)	
occurrences (all)	5	7	
Leukocytosis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	1 / 38 (2.63%)	5 / 36 (13.89%)	
occurrences (all)	1	5	
Thrombocytopenia			
subjects affected / exposed	8 / 38 (21.05%)	7 / 36 (19.44%)	
occurrences (all)	8	7	
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 38 (7.89%)	1 / 36 (2.78%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	6 / 38 (15.79%)	11 / 36 (30.56%)	
occurrences (all)	6	11	
Abdominal pain upper			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	6 / 38 (15.79%)	3 / 36 (8.33%)	
occurrences (all)	6	3	
Diarrhoea			

subjects affected / exposed	10 / 38 (26.32%)	12 / 36 (33.33%)	
occurrences (all)	10	12	
Dyspepsia			
subjects affected / exposed	6 / 38 (15.79%)	2 / 36 (5.56%)	
occurrences (all)	6	2	
Eructation			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Haematemesis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	2 / 38 (5.26%)	3 / 36 (8.33%)	
occurrences (all)	2	3	
Mouth haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	10 / 38 (26.32%)	16 / 36 (44.44%)	
occurrences (all)	10	16	
Proctalgia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Toothache			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	11 / 38 (28.95%)	12 / 36 (33.33%)	
occurrences (all)	11	12	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 38 (7.89%)	1 / 36 (2.78%)	
occurrences (all)	3	1	

Erythema			
subjects affected / exposed	0 / 38 (0.00%)	4 / 36 (11.11%)	
occurrences (all)	0	4	
Night sweats			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Petechiae			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Pruritus			
subjects affected / exposed	3 / 38 (7.89%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Rash			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Rash erythematous			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Rash maculo-papular			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Skin lesion			
subjects affected / exposed	3 / 38 (7.89%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Urinary hesitation			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Urinary incontinence			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 38 (7.89%)	2 / 36 (5.56%)	
occurrences (all)	3	2	
Back pain			
subjects affected / exposed	5 / 38 (13.16%)	3 / 36 (8.33%)	
occurrences (all)	5	3	
Muscular weakness			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	2 / 38 (5.26%)	6 / 36 (16.67%)	
occurrences (all)	2	6	
Myalgia			
subjects affected / exposed	4 / 38 (10.53%)	1 / 36 (2.78%)	
occurrences (all)	4	1	
Neck pain			
subjects affected / exposed	1 / 38 (2.63%)	4 / 36 (11.11%)	
occurrences (all)	1	4	
Pain in extremity			
subjects affected / exposed	3 / 38 (7.89%)	3 / 36 (8.33%)	
occurrences (all)	3	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Clostridial infection			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Clostridium difficile colitis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Herpes simplex			

subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	0 / 38 (0.00%)	5 / 36 (13.89%)	
occurrences (all)	0	5	
Pneumonia fungal			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Rhinitis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Vaginal infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 38 (13.16%)	6 / 36 (16.67%)	
occurrences (all)	5	6	
Hyperglycaemia			
subjects affected / exposed	4 / 38 (10.53%)	3 / 36 (8.33%)	
occurrences (all)	4	3	
Hyperkalaemia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Hyperphosphataemia			
subjects affected / exposed	0 / 38 (0.00%)	6 / 36 (16.67%)	
occurrences (all)	0	6	
Hypoalbuminaemia			
subjects affected / exposed	4 / 38 (10.53%)	2 / 36 (5.56%)	
occurrences (all)	4	2	

Hypocalcaemia			
subjects affected / exposed	4 / 38 (10.53%)	2 / 36 (5.56%)	
occurrences (all)	4	2	
Hypokalaemia			
subjects affected / exposed	9 / 38 (23.68%)	6 / 36 (16.67%)	
occurrences (all)	9	6	
Hypomagnesaemia			
subjects affected / exposed	5 / 38 (13.16%)	4 / 36 (11.11%)	
occurrences (all)	5	4	
Hyponatraemia			
subjects affected / exposed	4 / 38 (10.53%)	2 / 36 (5.56%)	
occurrences (all)	4	2	
Hypophosphataemia			
subjects affected / exposed	1 / 38 (2.63%)	5 / 36 (13.89%)	
occurrences (all)	1	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2012	• Updated the Sponsor address. • Updated contact details of key Sponsor's personnel. • Corrected the compound code for the active metabolite of AC220. • Revised inclusion criteria. • Updated and clarified exclusion criteria. • Revised significance level in statistics section. • Updated stopping table in statistics section. • Updated Table 1 and footnotes. • Updated Table 2 and footnotes. • Clarifies that MUGA or ECHO is allowed at Screening. • Updated the formulation of the investigational drug is supplied as 90 mg of AC220. • Updated the storage temperature of AC220. • Updated the time of stability for reconstituted AC220. • Defined AE reporting time. • Clarified the requirements on when to include height and weight during physical exams. • Updated the title of sections 5.7.1.2 and 5.7.1.3. • Updated the total amount of blood required for the study. • Updated Appendix 12.10. • Included other minor administrative-type corrections, eg, consistency, format, typos, etc.
22 October 2012	• Updated the List of Abbreviations. • Updated secondary objectives. • Revised sample size. • Clarified that MUGA or ECHO is allowed at Screening. • Clarified the screening assessments that require bone marrow samples. • Revised inclusion criteria. • Revised exclusion criteria. • Clarified CR definition. • Clarified and corrected QTcF grading definition. • Updated and clarified exploratory variables. • Clarified efficacy analysis based on central versus local FLT3-ITD testing. • Added central morphological review of bone marrow samples. • Revised language in efficacy, safety and PK analysis sections. • Updated footnote in Table 1. • Updated clinical information from AC220-002 clinical study. • Clarified AC220 dose re-escalation language. • Updated concomitant medication section. • Added instructions to be followed in the case of a missed dosage. • Clarified criteria for continuation of treatment. • Added text describing secondary efficacy objectives. • Added text on disease history and extent of exposure. • Updated language about secondary safety analysis. • Added text on previous and concomitant transfusions. • Updated pharmacodynamic analyses section. • Included information on protocol deviations. • Clarified use of a Data Monitoring Committee. • Added missing CYP3A4 inhibitors to the list of excluded concomitant medication. • Clarified lines of therapy and add tools for patient eligibility determination. • Included other minor administrative-type corrections, eg, consistency, format, typos, etc.

28 August 2013	• Changed headers and footers. • Changed title page format. • Changed IND and EudraCT numbers. • Removed Astellas terminology. • Removed reference to Astellas. • Removed reference to Astellas personnel.
04 October 2014	• EudraCT number was corrected. • Contact details of key Sponsor personnel were updated (Section II). • Planned study period was updated (Section IV). • Description of study drug was updated to include both powder and tablet formulations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported