Clinical trial results:
Randomised phase II trial of cediranib (AZD2171) vs. placebo in addition to cisplatin / gemcitabine chemotherapy for patients with advanced biliary tract cancers

Summary

EudraCT number	2009-013408-30
Trial protocol	GB
Global end of trial date	29 September 2014

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	UCL/09/0193

Additional study identifiers

ISRCTN number	ISRCTN34043997
ClinicalTrials.gov id (NCT number)	NCT00939848
WHO universal trial number (UTN)	-
Other trial identifiers	Funder Reference: C2930/A11428, MHRA CTA No.: 20363/0283/001-0001, Study Acronym: ABC-03

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Public Contact, CR UK & UCL Cancer Trials Centre , ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific Contact, CR UK & UCL Cancer Trials Centre , ctc.sponsor@ucl.ac.uk

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	29 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2014
Global end of trial reached?	Yes
Global end of trial date	29 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy and safety of cediranib in combination with cisplatin + gemcitabine (CisGem) chemotherapy compared to CisGem and placebo.

Protection of trial subjects:

Hypertension was a known side effect of cediranib and a detailed plan for management of hypertension was included in the trial protocol. In general, patients were monitored closely for side effects and the protocol contained management plans to prevent or treat side effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2011
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 Kingdom: 124
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	55
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

124 patients were recruited into the ABC-03 trial (62 in each arm) between 20 April 2011 and 28 September 2012. Participants were recruited from 14 participating hospitals in the United Kingdom.

Pre-assignment

Screening details:

All eligibility criteria were based on routine tests and investigations.

Period 1

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

Blinding implementation details:

At randomisation patients were allocated a trial ID which was linked to their treatment allocation. The pateints trial ID was used to dispense the appropriate trial medication (cedrianib or placebo) using an interactive web based response system (IWRS). None of the treating clinician, pharmacist nor the pateint were aware of which treatment the patient was receiving. Cediranib and placebo bottles were labelled in a blinded manner.

Arms

Are arms mutually exclusive?	Yes
Arm title	The control arm (Arm A)

Arm description:

Patients on the control arm (Arm A) recieved cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 (CisGem) on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded placebo tablets taken once daily every day (continuous dosing).

Arm type	Placebo
Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Intravenous use

Dosage and administration details:

cisplatin 25mg/m2 on days 1 and 8 of a 21 day cycle for 8 cycles

Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

gemcitabine on days 1 and 8 of a 21 day cycle for 8 cycles

Arm title	The experimental arm (Arm B)

Arm description:

Patients on the experimental arm (Arm B) received cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded cediranib 20 mg tablets taken once daily every day (continuous dosing).

Arm type	Experimental

Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Blinded cediranib 20 mg tablets taken once daily every day (continuous dosing).

Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Intravenous use

Dosage and administration details:

cisplatin 25mg/m2 on days 1 and 8 of a 21 day cycle for 8 cycles

Investigational medicinal product name	gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

gemcitabine on days 1 and 8 of a 21 day cycle for 8 cycles

Number of subjects in period 1	The control arm (Arm A)	The experimental arm (Arm B)
Started	62	62
Completed	29	29
Not completed	33	33
Physician decision	2	2
toxicity	5	16
Did not start intervention (not fit for treatment)	2	-
disease progression	18	9
patient decision	2	1
symptomatic deterioration	4	5

Baseline characteristics

Reporting groups	
Reporting group title	The control arm (Arm A)
Reporting group description:	
Patients on the control arm (Arm A) recieved cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 (CisGem) on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded placebo tablets taken once daily every day (continuous dosing).	
Reporting group title	The experimental arm (Arm B)
Reporting group description:	
Patients on the experimental arm (Arm B) received cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded cediranib 20 mg tablets taken once daily every day (continuous dosing).	

Reporting group values	The control arm (Arm A)	The experimental arm (Arm B)	Total
Number of subjects	62	62	124
Age categorical Units: Subjects			
Adults (18-64 years)	34	21	55
From 65-84 years	28	41	69
85 years and over	0	0	0
Age continuous			
Eligible patients were aged ≥18 years with a histopathological/cytological diagnosis of non-resectable, recurrent or metastatic biliary tract carcinoma (intra- or extra-hepatic cholangiocarcinoma), gallbladder or ampullary carcinoma.			
Units: years			
median	64.5	68	
inter-quartile range (Q1-Q3)	59.7 to 73.1	60.4 to 73	-
Gender categorical Units: Subjects			
Female	34	28	62
Male	28	34	62
Primary Tumour Site Units: Subjects			
Cholangiocarcinoma - Intrahepatic	15	14	29
Cholangiocarcinoma - Extrahepatic	24	24	48
Gallbladder	19	20	39
Ampulla	4	4	8
Histological grade Units: Subjects			
Well differentiated	27	26	53
Moderately differentiated	21	20	41
Poorly differentiated	13	13	26
Not specified	1	3	4
Prior therapy Units: Subjects			
Adjuvant chemotherapy	1	2	3
Other	22	23	45
None	39	37	76
ECOG performance status			

Units: Subjects			
ECOG 0	28	27	55
ECOG 1	34	35	69
Disease status Units: Subjects			
Locally advanced	8	12	20
metastatic	54	50	104
CA19-9 median (IQR) IU/mL Units: IU/mL			
median	53	298	
inter-quartile range (Q1-Q3)	10 to 492	38 to 2258	-

End points

End points reporting groups

Reporting group title	The control arm (Arm A)

Reporting group description:

Patients on the control arm (Arm A) recieved cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 (CisGem) on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded placebo tablets taken once daily every day (continuous dosing).

Reporting group title	The experimental arm (Arm B)

Reporting group description:

Patients on the experimental arm (Arm B) received cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded cediranib 20 mg tablets taken once daily every day (continuous dosing).

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Primary

End point timeframe:

Overall Trial

End point values	The control arm (Arm A)	The experimental arm (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	59		
Units: Months				
median (confidence interval 95%)	7.4 (5.7 to 8.5)	8 (6.5 to 9.3)		

Statistical analyses

Statistical analysis title	Progression-free survival

Statistical analysis description:

The trial was designed to directly compare progression free survival between the two treatment groups, with 80% power and a two-sided alpha of 0·2, to detect a progression-free survival hazard ratio (HR) of 0·64. This required a sample size of 68 per group. The main analysis involved estimating the HR, 80% CI, and p value. If the HR was less than 1 and the p value was less than 0·2, the study would be deemed to have provided sufficient evidence to do a larger trial.

Comparison groups	The experimental arm (Arm B) v The control arm (Arm A)

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.2
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.51
upper limit	0.77

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Overall Trial

End point values	The control arm (Arm A)	The experimental arm (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Months				
median (confidence interval 95%)	11.9 (9.2 to 14.3)	14.1 (10.2 to 16.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response (RECIST v1.1)

End point title	Best overall response (RECIST v1.1)

End point description:

End point type	Secondary

End point timeframe:

Overall Trial

End point values	The control arm (Arm A)	The experimental arm (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	59		
Units: Patients				
Complete Response (CR)	0	2		
Partial Response (PR)	10	24		
Stable Disease (SD)	25	20		
Response Rate (CR+PR)	10	26		
Disease Control Rate (CR+PR+SD)	35	46		
Progressive Disease (PD)	15	6		
Unknown	4	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events

End point title	Adverse Events

End point description:

End point type	Secondary

End point timeframe:

Overall Trial

End point values	The control arm (Arm A)	The experimental arm (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Patients	62	62		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall Trial

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	The control arm (Arm A)

Reporting group description:

The control arm (Arm A) consisted of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 (CisGem) on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded placebo tablets taken once daily every day (continuous dosing).

Reporting group title	The experimental arm (Arm B)

Reporting group description:

The experimental arm (Arm B) consisted of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 on days 1 and 8 of a 21-day cycle for up to 8 cycles with blinded cediranib 20 mg tablets taken once daily every day (continuous dosing).

Serious adverse events	The control arm (Arm A)	The experimental arm (Arm B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 62 (61.29%)	42 / 62 (67.74%)	
number of deaths (all causes)	61	61	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 62 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 62 (3.23%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 62 (3.23%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thromboembolic event			

subjects affected / exposed	5 / 62 (8.06%)	5 / 62 (8.06%)	
occurrences causally related to treatment / all	4 / 5	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
other, Cerebral Bleed			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
other, blocked biliary stent			
subjects affected / exposed	2 / 62 (3.23%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	5 / 62 (8.06%)	14 / 62 (22.58%)	
occurrences causally related to treatment / all	6 / 8	7 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 62 (1.61%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			

subjects affected / exposed	1 / 62 (1.61%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 62 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 62 (1.61%)	5 / 62 (8.06%)	
occurrences causally related to treatment / all	1 / 1	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	1 / 62 (1.61%)	6 / 62 (9.68%)	
occurrences causally related to treatment / all	1 / 1	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell decreased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chest pain - cardiac			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
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	0 / 62 (0.00%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pericardial effusion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disturbance			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (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 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			

subjects affected / exposed	1 / 62 (1.61%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Syncope			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
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	0 / 62 (0.00%)	4 / 62 (6.45%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 62 (0.00%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 62 (1.61%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 62 (4.84%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	2 / 62 (3.23%)	6 / 62 (9.68%)	
occurrences causally related to treatment / all	1 / 2	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			
subjects affected / exposed	1 / 62 (1.61%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 62 (3.23%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (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	8 / 62 (12.90%)	5 / 62 (8.06%)	
occurrences causally related to treatment / all	4 / 8	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
other, Hemorrhage NOS			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other, degenerative disc changes			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (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			
Biliary tract infection			
subjects affected / exposed	1 / 62 (1.61%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			

subjects affected / exposed	3 / 62 (4.84%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (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	2 / 62 (3.23%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 62 (4.84%)	6 / 62 (9.68%)	
occurrences causally related to treatment / all	1 / 3	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 62 (4.84%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
other, Infection and infestations source not known			
subjects affected / exposed	4 / 62 (6.45%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	3 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 62 (0.00%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 62 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 62 (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	The control arm (Arm A)	The experimental arm (Arm B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 62 (100.00%)	62 / 62 (100.00%)	
Vascular disorders			
Hot flashes			
subjects affected / exposed	6 / 62 (9.68%)	1 / 62 (1.61%)	
occurrences (all)	6	1	
Hypertension			
subjects affected / exposed	30 / 62 (48.39%)	42 / 62 (67.74%)	
occurrences (all)	30	42	
Hypotension			
subjects affected / exposed	5 / 62 (8.06%)	2 / 62 (3.23%)	
occurrences (all)	5	2	
Superficial thrombophlebitis			
subjects affected / exposed	4 / 62 (6.45%)	1 / 62 (1.61%)	
occurrences (all)	4	1	
Thromboembolic Event			
subjects affected / exposed	9 / 62 (14.52%)	7 / 62 (11.29%)	
occurrences (all)	9	7	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 62 (3.23%)	5 / 62 (8.06%)	
occurrences (all)	2	5	
Edema limbs			

subjects affected / exposed	17 / 62 (27.42%)	22 / 62 (35.48%)	
occurrences (all)	17	22	
Fatigue			
subjects affected / exposed	47 / 62 (75.81%)	52 / 62 (83.87%)	
occurrences (all)	47	52	
Fever			
subjects affected / exposed	17 / 62 (27.42%)	24 / 62 (38.71%)	
occurrences (all)	17	24	
Flu like symptoms			
subjects affected / exposed	12 / 62 (19.35%)	12 / 62 (19.35%)	
occurrences (all)	12	12	
General disorders other - Night sweats			
subjects affected / exposed	3 / 62 (4.84%)	2 / 62 (3.23%)	
occurrences (all)	3	2	
Non-cardiac chest pain			
subjects affected / exposed	6 / 62 (9.68%)	2 / 62 (3.23%)	
occurrences (all)	6	2	
Pain			
subjects affected / exposed	29 / 62 (46.77%)	30 / 62 (48.39%)	
occurrences (all)	29	30	
Pruritus			
subjects affected / exposed	3 / 62 (4.84%)	3 / 62 (4.84%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 62 (12.90%)	13 / 62 (20.97%)	
occurrences (all)	8	13	
Dyspnea			
subjects affected / exposed	19 / 62 (30.65%)	16 / 62 (25.81%)	
occurrences (all)	19	16	
Epistaxis			
subjects affected / exposed	6 / 62 (9.68%)	17 / 62 (27.42%)	
occurrences (all)	6	17	
Hiccups			

subjects affected / exposed	2 / 62 (3.23%)	3 / 62 (4.84%)	
occurrences (all)	2	3	
Sore Throat			
subjects affected / exposed	6 / 62 (9.68%)	11 / 62 (17.74%)	
occurrences (all)	6	11	
Psychiatric disorders			
Depression			
subjects affected / exposed	6 / 62 (9.68%)	1 / 62 (1.61%)	
occurrences (all)	6	1	
Insomnia			
subjects affected / exposed	12 / 62 (19.35%)	11 / 62 (17.74%)	
occurrences (all)	12	11	
Anxiety			
subjects affected / exposed	1 / 62 (1.61%)	3 / 62 (4.84%)	
occurrences (all)	1	3	
Investigations			
Platelet count decreased			
subjects affected / exposed	32 / 62 (51.61%)	44 / 62 (70.97%)	
occurrences (all)	32	44	
White blood cell count decreased			
subjects affected / exposed	39 / 62 (62.90%)	43 / 62 (69.35%)	
occurrences (all)	39	43	
Neutrophil count decreased			
subjects affected / exposed	43 / 62 (69.35%)	48 / 62 (77.42%)	
occurrences (all)	43	48	
Creatinine increased			
subjects affected / exposed	10 / 62 (16.13%)	17 / 62 (27.42%)	
occurrences (all)	10	17	
GGT increased			
subjects affected / exposed	54 / 62 (87.10%)	61 / 62 (98.39%)	
occurrences (all)	54	61	
Alanine aminotransferase increased			
subjects affected / exposed	43 / 62 (69.35%)	50 / 62 (80.65%)	
occurrences (all)	43	50	
Alkaline phosphatase increased			

subjects affected / exposed	47 / 62 (75.81%)	47 / 62 (75.81%)	
occurrences (all)	47	47	
Aspartate aminotransferase increased			
subjects affected / exposed	37 / 62 (59.68%)	43 / 62 (69.35%)	
occurrences (all)	37	43	
Blood bilirubin increased			
subjects affected / exposed	13 / 62 (20.97%)	12 / 62 (19.35%)	
occurrences (all)	13	12	
Weight loss			
subjects affected / exposed	4 / 62 (6.45%)	12 / 62 (19.35%)	
occurrences (all)	4	12	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	2 / 62 (3.23%)	3 / 62 (4.84%)	
occurrences (all)	2	3	
Nervous system disorders			
Cognitive disturbance			
subjects affected / exposed	1 / 62 (1.61%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
Dizziness			
subjects affected / exposed	8 / 62 (12.90%)	6 / 62 (9.68%)	
occurrences (all)	8	6	
Dysgeusia			
subjects affected / exposed	19 / 62 (30.65%)	20 / 62 (32.26%)	
occurrences (all)	19	20	
Lethargy			
subjects affected / exposed	42 / 62 (67.74%)	43 / 62 (69.35%)	
occurrences (all)	42	43	
Peripheral sensory neuropathy			
subjects affected / exposed	16 / 62 (25.81%)	16 / 62 (25.81%)	
occurrences (all)	16	16	
Presyncope			
subjects affected / exposed	4 / 62 (6.45%)	3 / 62 (4.84%)	
occurrences (all)	4	3	
Seizure			

subjects affected / exposed	0 / 62 (0.00%)	3 / 62 (4.84%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	57 / 62 (91.94%)	59 / 62 (95.16%)	
occurrences (all)	57	59	
Febrile neutropenia			
subjects affected / exposed	1 / 62 (1.61%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
Ear and labyrinth disorders			
Hearing Impaired			
subjects affected / exposed	7 / 62 (11.29%)	3 / 62 (4.84%)	
occurrences (all)	7	3	
Tinnitus			
subjects affected / exposed	9 / 62 (14.52%)	4 / 62 (6.45%)	
occurrences (all)	9	4	
Eye disorders			
Blurred vision			
subjects affected / exposed	2 / 62 (3.23%)	3 / 62 (4.84%)	
occurrences (all)	2	3	
Eye pain			
subjects affected / exposed	0 / 62 (0.00%)	3 / 62 (4.84%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 62 (3.23%)	5 / 62 (8.06%)	
occurrences (all)	2	5	
Abdominal pain			
subjects affected / exposed	32 / 62 (51.61%)	32 / 62 (51.61%)	
occurrences (all)	32	32	
Ascites			
subjects affected / exposed	1 / 62 (1.61%)	3 / 62 (4.84%)	
occurrences (all)	1	3	
Bloating			
subjects affected / exposed	4 / 62 (6.45%)	1 / 62 (1.61%)	
occurrences (all)	4	1	
Constipation			

subjects affected / exposed	42 / 62 (67.74%)	42 / 62 (67.74%)	
occurrences (all)	42	42	
Diarrhoea			
subjects affected / exposed	24 / 62 (38.71%)	45 / 62 (72.58%)	
occurrences (all)	24	45	
Dry mouth			
subjects affected / exposed	8 / 62 (12.90%)	15 / 62 (24.19%)	
occurrences (all)	8	15	
Dyspepsia			
subjects affected / exposed	7 / 62 (11.29%)	13 / 62 (20.97%)	
occurrences (all)	7	13	
Flatulence			
subjects affected / exposed	6 / 62 (9.68%)	7 / 62 (11.29%)	
occurrences (all)	6	7	
Gastroesophageal relux disease			
subjects affected / exposed	17 / 62 (27.42%)	10 / 62 (16.13%)	
occurrences (all)	17	10	
Mucositis oral			
subjects affected / exposed	13 / 62 (20.97%)	25 / 62 (40.32%)	
occurrences (all)	13	25	
Nausea			
subjects affected / exposed	43 / 62 (69.35%)	43 / 62 (69.35%)	
occurrences (all)	43	43	
Toothache			
subjects affected / exposed	0 / 62 (0.00%)	3 / 62 (4.84%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	30 / 62 (48.39%)	30 / 62 (48.39%)	
occurrences (all)	30	30	
Hepatobiliary disorders			
Hepatobiliary disorder other - biliary obstruction			
subjects affected / exposed	4 / 62 (6.45%)	0 / 62 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	18 / 62 (29.03%)	10 / 62 (16.13%)	
occurrences (all)	18	10	
Dry skin			
subjects affected / exposed	4 / 62 (6.45%)	1 / 62 (1.61%)	
occurrences (all)	4	1	
Hyperhidrosis			
subjects affected / exposed	1 / 62 (1.61%)	3 / 62 (4.84%)	
occurrences (all)	1	3	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	3 / 62 (4.84%)	5 / 62 (8.06%)	
occurrences (all)	3	5	
Papulopustular rash			
subjects affected / exposed	3 / 62 (4.84%)	7 / 62 (11.29%)	
occurrences (all)	3	7	
Rash maculo-papular			
subjects affected / exposed	6 / 62 (9.68%)	12 / 62 (19.35%)	
occurrences (all)	6	12	
Skin ulceration			
subjects affected / exposed	0 / 62 (0.00%)	3 / 62 (4.84%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Urinary frequency			
subjects affected / exposed	3 / 62 (4.84%)	2 / 62 (3.23%)	
occurrences (all)	3	2	
Urinary tract pain			
subjects affected / exposed	0 / 62 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 62 (8.06%)	4 / 62 (6.45%)	
occurrences (all)	5	4	
Back pain			
subjects affected / exposed	11 / 62 (17.74%)	15 / 62 (24.19%)	
occurrences (all)	11	15	
Generalised muscle weakness			

subjects affected / exposed	6 / 62 (9.68%)	13 / 62 (20.97%)	
occurrences (all)	6	13	
Myalgia			
subjects affected / exposed	11 / 62 (17.74%)	7 / 62 (11.29%)	
occurrences (all)	11	7	
Neck pain			
subjects affected / exposed	3 / 62 (4.84%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	6 / 62 (9.68%)	8 / 62 (12.90%)	
occurrences (all)	6	8	
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	3 / 62 (4.84%)	8 / 62 (12.90%)	
occurrences (all)	3	8	
Infection			
subjects affected / exposed	7 / 62 (11.29%)	3 / 62 (4.84%)	
occurrences (all)	7	3	
Lung infection			
subjects affected / exposed	11 / 62 (17.74%)	4 / 62 (6.45%)	
occurrences (all)	11	4	
Mucosal infection			
subjects affected / exposed	3 / 62 (4.84%)	6 / 62 (9.68%)	
occurrences (all)	3	6	
Sepsis			
subjects affected / exposed	3 / 62 (4.84%)	6 / 62 (9.68%)	
occurrences (all)	3	6	
Skin infection			
subjects affected / exposed	3 / 62 (4.84%)	1 / 62 (1.61%)	
occurrences (all)	3	1	
Upper respiratory infection			
subjects affected / exposed	9 / 62 (14.52%)	15 / 62 (24.19%)	
occurrences (all)	9	15	
Urinary tract infection			
subjects affected / exposed	7 / 62 (11.29%)	9 / 62 (14.52%)	
occurrences (all)	7	9	

Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	22 / 62 (35.48%)	27 / 62 (43.55%)	
occurrences (all)	22	27	
Hypoalbuminaemia			
subjects affected / exposed	23 / 62 (37.10%)	31 / 62 (50.00%)	
occurrences (all)	23	31	
Hypomagnesaemia			
subjects affected / exposed	21 / 62 (33.87%)	30 / 62 (48.39%)	
occurrences (all)	21	30	
Hypophosphataemia			
subjects affected / exposed	19 / 62 (30.65%)	25 / 62 (40.32%)	
occurrences (all)	19	25	
Hyponatraemia			
subjects affected / exposed	32 / 62 (51.61%)	36 / 62 (58.06%)	
occurrences (all)	32	36	
Hypokalaemia			
subjects affected / exposed	18 / 62 (29.03%)	21 / 62 (33.87%)	
occurrences (all)	18	21	
Anorexia			
subjects affected / exposed	27 / 62 (43.55%)	43 / 62 (69.35%)	
occurrences (all)	27	43	
Dehydration			
subjects affected / exposed	2 / 62 (3.23%)	3 / 62 (4.84%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/2617920