Clinical trial results:
A Randomised Phase II Study Evaluating Cediranib vs. Cediranib and Saracatanib in patients with relapsed metastatic clear cell renal cancer

Summary

EudraCT number	2009-018014-20
Trial protocol	GB
Global end of trial date	12 December 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016
Summary attachment (see zip file)	COSAK Final Report (COSAK Final Report 22_Jan_16.pdf)

Trial information

Trial identification

Sponsor protocol code	COSAKV1

Additional study identifiers

ISRCTN number	ISRCTN56886343
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Research Ethics Committe Reference: 10/H0808/14

Notes:

Sponsors

Sponsor organisation name	Common Services Agency
Sponsor organisation address	South Gyle Crescent, Edinburgh, United Kingdom, EH12 9EB
Public contact	Dr Joanna Dunlop, Scottish Clinical Trials Research Unit, 0131 275 7178, joanna.dunlop@nhs.net
Scientific contact	Professor Thomas Powles, St Bartholomew's Hospital, thomas.powles@bartshealth.nhs.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	15 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 January 2014
Global end of trial reached?	Yes
Global end of trial date	12 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary research objective is to see whether patients taking cediranib in combination with saracatanib have a longer progression free survival (surviving without their cancer returning or relapsing) than the patients who are taking cediranib with placebo.

Protection of trial subjects:

Laboratory tests were performed at baseline and throughout the study including measurement of serum chemistry and haematology values (sodium, potassium, urea, creatinine, bilirubin, AST and/or ALT, alkaline phosphatase, LDH, albumin, total protein, calcium, phosphate, Hb, WCC, ANC, platelets and TSH). Any clinically significant laboratory abnormalities were recorded as adverse events. Patients were assessed by the investigator to determine if the abnormal finding was sufficient to immediately withdraw the patients from the study. Any laboratory value that met the definition of Serious Adverse Event must be reported as an SAE. In addition, the patient was reassessed for continuation in the study and any indicated and appropriate therapies should be initiated.

In addition to the laboratory test, blood pressure was regularly monitored throughout the trial to identify treatment related hypertension, a hypertension management protocol for emergency hypertension was put in place.

Data was reviewed 6 months after the first patient entered the study by the DMC, who assess the data primarily from the stand-point of safety and treatment deliverability.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	02 September 2010
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: 138
Worldwide total number of subjects	138
EEA total number of subjects	138

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	91
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 02 September 2010 - 26 January 2012

Uk sites only

Pre-assignment

Screening details:

204 patients were screened. Sixty-six screening failures. Brain metastases, worsening performance status and inadequate organ function were common reasons for exclusion.

Period 1

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

Blinding implementation details:

At each site only the investigator and trial pharmacist have access to this system to unblind the patient. In an emergency if these two individuals are unavailable a 24 hour helpline was available. In this case it would be the Chief Investigator who would advise if unblinding could go ahead.
Treatment codes are only broken in medical emergencies when appropriate management of the patient necessitates knowledge of the treatment randomisation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cediranib and Saracatinib

Arm description:

Combination cediranib 30mg once daily and saracatinib 175mg once daily.

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

Dosage and administration details:

175mg once daily

Arm title	Cediranib and placebo

Arm description:

Cediranib chemotherapy regime plus placebo

Arm type	Active comparator
Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30mg od

Number of subjects in period 1	Cediranib and Saracatinib	Cediranib and placebo
Started	69	69
Completed	69	69

Baseline characteristics

End points

End points reporting groups

Reporting group title	Cediranib and Saracatinib
Reporting group description:	
Combination cediranib 30mg once daily and saracatinib 175mg once daily.	
Reporting group title	Cediranib and placebo
Reporting group description:	
Cediranib chemotherapy regime plus placebo	

Primary: The primary outcome is to investigate the progression free survival of the combination of cediranib and saracatinib compared to cediranib alone.

End point title	The primary outcome is to investigate the progression free survival of the combination of cediranib and saracatinib compared to cediranib alone.
End point description:	
End point type	Primary
End point timeframe:	
Patients were randomised to receive study drug until progression of disease, death, excess toxicity or discontinuation for another reason. Radiological assessment (RECIST v1.1) occurred eight weekly until progression.	

End point values	Cediranib and Saracatinib	Cediranib and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	69		
Units: years				
median (standard error)	0.455 (± 0.08)	0.323 (± 0.063)		

Statistical analyses

Statistical analysis title	Efficacy analysis
Statistical analysis description:	
A Kaplan-Meier plot of progression free survival was presented. The median progression free survival time for each study arm was tabulated together with the corresponding 80% confidence interval. The corresponding hazard ratio and 80% confidence interval and 1-sided p-value associated with the comparison of the treatment arms from the Cox model fitted to the data was reported. This is the primary comparison.	
Comparison groups	Cediranib and Saracatinib v Cediranib and placebo

Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.179
Confidence interval	
level	Other: 0.8 %
sides	1-sided
lower limit	0.94
Variability estimate	Standard error of the mean
Dispersion value	0.177

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any time between start of first treatment and within 30 days after administration of last dose of study drug.

Adverse event reporting additional description:

All laboratory values were coded according to the CTC toxicity criteria and the worst value over the study drug periods was determined for each patient. All adverse events were similarly coded.

NOTE that this study uses a 10% reporting threshold although this system would only allow a max value of 5%.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Cediranib and Saracatinib

Reporting group description:

Combination cediranib 30mg once daily and saracatinib 175mg once daily.

Reporting group title	Cediranib and placebo

Reporting group description:

Cediranib chemotherapy regime plus placebo

Serious adverse events	Cediranib and Saracatinib	Cediranib and placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 68 (48.53%)	29 / 68 (42.65%)	
number of deaths (all causes)	58	60	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain - cardiac			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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			
Neurological symptoms			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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			
Abdominal pain	Additional description: Acute abdominal pain		
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pontine haemorrhage	Additional description: Acute pontine haemorrhage leading to hospitalisation or prolongation of hospitalisation		
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peri-anal abscess	Additional description: Admission due to peri-anal abscess		
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergilloma			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain	Additional description: 1 event of 'Back pain' , 1 event of 'Back pain and abdominal pain', 1 event of 'Worsening back pain'		
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilateral leg weakness			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion	Additional description: 1 event of 'Confusion' and 1 event of 'Confusion secondary to urine infection'		
subjects affected / exposed	2 / 68 (2.94%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crampiform dull epigastric ache			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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	1 / 68 (1.47%)	8 / 68 (11.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fall			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General deterioration			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headaches and vomiting			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 68 (4.41%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low sodium			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occipital headache			

subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain control and drowsy			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Possible infected element			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-prostate biopsy sepsis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PR bleeding			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raised calcium			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Raised potassium			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced mobility			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
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	Additional description: Anaemia (low haemoglobin)		
subjects affected / exposed	3 / 68 (4.41%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Acute viral gastroenteritis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	6 / 68 (8.82%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	2 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe nausea and vomiting			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper GI bleed			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleed (2)			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Breathless	Additional description: Breathlessness		
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Shortness of breath		
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
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 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortness of breath			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver transaminase increase			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor renal function			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine retention			

subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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			
Fracture to left tibia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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			
Boil on buttock			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest infection			
subjects affected / exposed	4 / 68 (5.88%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia	Additional description: Hospital admittance with pneumonia		
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection (2)			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Urine tract infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (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	Cediranib and Saracatinib	Cediranib and placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 68 (100.00%)	68 / 68 (100.00%)	
General disorders and administration site conditions			
Lethargy			
subjects affected / exposed	68 / 68 (100.00%)	68 / 68 (100.00%)	
occurrences (all)	68	68	
Respiratory, thoracic and mediastinal disorders			
Mucositis			
subjects affected / exposed	68 / 68 (100.00%)	68 / 68 (100.00%)	
occurrences (all)	68	68	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2010	Changes to protocol and documents appended to the initial application. Changes in conduct or management of the trial. Change / addition of PI and sites.
15 June 2011	Addition of two new sites. Change of PI at existing site.
29 September 2011	Changes to protocol due to closure of sub-studies. Changes to Patient Information Sheet and Informed Consent form.
18 November 2013	Changes to protocol to redefine the 'End of Trial' and to document the Sponsor's obligations to patients still receiving study drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported