



## 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 Committee 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 saracatinib 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                       |
| <b>Arm title</b>             | 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

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b> | 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:<br>Combination cediranib 30mg once daily and saracatinib 175mg once daily. |                           |
| Reporting group title   | Cediranib and placebo     |
| Reporting group description:<br>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:<br>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 ( $\pm$ 0.08)       | 0.323 ( $\pm$ 0.063)  |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Efficacy analysis                                 |
| Statistical analysis description:<br>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 %

| <b>Non-serious adverse events</b>                     | 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.<br>Changes in conduct or management of the trial.<br>Change / addition of PI and sites. |
| 15 June 2011      | Addition of two new sites.<br>Change of PI at existing site.   |
| 29 September 2011 | Changes to protocol due to closure of sub-studies.<br>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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported