Clinical trial results:
A study of pazopanib efficacy and safety in patients with advanced clear-cell renal cell carcinoma and ECOG Performance Status 2 (PaZ02)

Summary

EudraCT number	2011-001211-31
Trial protocol	GB
Global end of trial date	30 June 2019

Results information

Result version number	v1 (current)
This version publication date	09 October 2020
First version publication date	09 October 2020

Trial information

Trial identification

Sponsor protocol code	RG_10-177

Additional study identifiers

ISRCTN number	ISRCTN38957238
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Dr Birgit Whitman, University of Birmingham, researchgovernance@contacts.bham.ac.uk
Scientific contact	Cancer Research UK Clinical Trials Unit (CRCTU) , University of Birmingham, crctu-generalenquiries@trials.bham.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	10 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of our clinical trial is to find out whether treatment with a drug called pazopanib is beneficial and safe for patients with advanced renal cancer and poor clinical condition (‘poor performance status’). These patients are often deemed not fit for treatment because of their poor prognosis and because of their perceived inability to withstand the side effects of the therapy. The treatments currently available cause severe side effects in two thirds of the patients and may require frequent hospital visits. By contrast pazopanib has demonstrated a significant efficacy and is well tolerated therefore it may represent a valuable treatment option for renal cancer patients with poor performance status. To assess treatment efficacy we will study in what percentage of patients pazopanib is able to prevent further tumour growth for at least 6 months; to assess safety we will study the ratio of patients who develop severe, drug induced, toxicity.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Site staff received GCP and trial specific training prior to recruiting patients to the study. A Data Monitoring Committee reviewed patient safety data throughout the trial. Additional measures were taken during the course of the study to monitor subject safety: (1) Medical history prior to registration to identify safety-related exclusion criteria, (2) Continuous assessment of adverse events and serious adverse events, (2) Haematology, biochemistry laboratory tests and urine dipstick test at regular intervals (2 weekly for the first 8 weeks, monthly thereafter during pazopanib treatment) (3) 8 weekly ECG with QTc measurement, (4) full review of body system through physical examination and vital signs assessment (2 weekly for the first 8 weeks, monthly thereafter during pazopanib treatment).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	21
From 65 to 84 years	53
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

26 UK sites took part in the study. The trial opened to recruitment in August 2012. The first participant was recruited into the trial on 21-Feb-2013. The recruitment rate was slower than anticipated and the trial reached its target of 75 patients in 42 months, with the last subject recruited on 12-Aug-2016.

Pre-assignment

Screening details:

Formal screening logs were requested. A total of 255 patients were considered for the trial, of these 75 were recruited and 180 subjects excluded. Main reasons for exclusion: 121 patients did not meet all entry criteria; 25 declined to participate; 27 were excluded for other clinical reasons; no reason was given for 7 patients.

Period 1

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

Arms

Arm title	Pazopanib

Arm description:

Patients who commenced Pazopanib treatment

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

Dosage and administration details:

800 mg OD, continuous dosing.

Number of subjects in period 1	Pazopanib
Started	75
Completed	65
Not completed	10
Consent withdrawn by subject	2
Ineligible post registration	2
Protocol deviation	6

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
Adults (18-64 years)	21	21	
From 65-84 years	53	53	
85 years and over	1	1	
Age continuous Units: years			
median	68.6		
inter-quartile range (Q1-Q3)	64.6 to 76.0	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	54	54	
Previous treatments Units: Subjects			
Radical nephrectomy only	25	25	
No prevous treatment	24	24	
Radical nephrectomy & radiotherapy	12	12	
Radiotherapy only	12	12	
Partial nephrectomy & radiotherapy	1	1	
Surgery only	1	1	
Metastases sites Units: Subjects			
Bone	7	7	
Bone & Liver	1	1	
Bone & Lung	6	6	
Bone & Other	1	1	
Bone, Liver & Lung	5	5	
Bone, Liver & Other	1	1	
Bone, Liver, Lung & Other	2	2	
Bone, Lung & Other	3	3	
Bone, Lymph & Lung	3	3	
Liver	1	1	
Liver & Lung	1	1	
Liver, Lung & Other	1	1	
Liver, Lymph & Lung	2	2	
Lung	22	22	
Lung & Other	2	2	
Lymph	1	1	
Lymph & Lung	5	5	

Lymph & Other	3	3	
Lymph, Lung & Other	3	3	
Other	5	5	
Clear Cell Component Units: Subjects			
No	1	1	
Yes	74	74	
Sarcomatoid component Units: Subjects			
No	66	66	
Yes	8	8	
Unknown	1	1	
T stage Units: Subjects			
TX	12	12	
T0	5	5	
T1	10	10	
T2	15	15	
T3	9	9	
T3a	10	10	
T3b	3	3	
T4	4	4	
T1a	1	1	
T1b	2	2	
T2a	1	1	
T2b	3	3	
N stage Units: Subjects			
NX	8	8	
N0	41	41	
N1	19	19	
N2	3	3	
Unknown	4	4	
M stage Units: Subjects			
M0	4	4	
M1	69	69	
Unknown	2	2	
Fuhrman grade Units: Subjects			
Grade 2	23	23	
Grade 3	20	20	
Grade 4	17	17	
Unknown	15	15	
Time from diagnosis to development of metastases Units: months			
median	0.8		
inter-quartile range (Q1-Q3)	0.0 to 28.1	-	
Time from diagnosis to registration Units: Years			
median	0.3		

inter-quartile range (Q1-Q3)	0.1 to 3.4	-	

End points

End points reporting groups

Reporting group title	Pazopanib
Reporting group description:	
Patients who commenced Pazopanib treatment	

Primary: Tolerability

End point title	Tolerability[1]

End point description:

Tolerability is defined as the proportion of patients who have not developed 'intolerable' adverse events within 183 days (6 months) from the date of registration.
Adverse events deemed 'Intolerable' must meet all the following criteria:
1. Grade 3 or 4 according to CTCAE version 4 AND
2. Rated as being possible, probably or definitely related to Pazopanib by the investigator AND
3. Result in either a Serious Adverse Event (SAE) OR discontinuation of pazopanib for a period greater than 21 days.
In cases where the adverse event meeting criteria 1 and 2 result in an SAE, the date of onset of the SAE is used as the date deemed intolerable. For those which result in pazopanib discontinuation, the first day that treatment was stopped is the intolerable date.
Patients who died prior to completing 6 months of treatment without having an event which meets the tolerability criteria are counted as tolerable and included in the denominator.

End point type	Primary

End point timeframe:

183 days (6 months) from the date of registration

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm phase II study looking at efficacy and toxicity. No statistical hypothesis testing was planned.

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Patients	46			

Statistical analyses

No statistical analyses for this end point

Primary: Efficacy

End point title	Efficacy[2]

End point description:

Efficacy is the proportion of patients who are radiologically progression free and alive at 6 months. Progression is defined in terms of RECIST 1.1 and it is also assumed that all deaths will be disease related and thus constitute progression. If multiple scans are done within the time frame the closest to day 183 will be used.
If no scan occurs within this time frame and the patient is alive and no prior progression has been reported then the following rules will be applied to determine whether the patient should be excluded from the analysis.

- In addition to the baseline scan if the patient has two scans (one before the time frame and one

after) that show the same response this will be taken as the response at 6 months and used in the analysis
• If the patient does not have scan either side of the time frame or if the response on those scans differs then it is impossible to say with any certainty what the response was at 6 months and this patient will be excluded.

End point type	Primary

End point timeframe:

The efficacy part of the primary outcome is reliant on recist data obtained from a scan at 6 months (183 days) post registration. A window of between 162 and 204 days is allowed for the scan to take place.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm phase II study looking at efficacy and toxicity. No statistical hypothesis testing was planned.

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Patients	37			

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rate

End point title	Response Rate

End point description:

This is defined as the proportion of patients who achieve a Complete or Partial radiological response during the study.

End point type	Secondary

End point timeframe:

Any point during the study

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Patients	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate

End point title	Clinical Benefit Rate

End point description:

The proportion of patients achieving Complete Response, Partial Response or Stable Disease during the

study.

End point type	Secondary

End point timeframe:

Any point during the study

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Patients	62			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival time

End point title	Progression free survival time

End point description:

Defined as the number of whole days from the date of registration until evidence of radiological disease progression or death from any cause. Patients who are alive and progression free will be censored at the date last known to be progression free.

End point type	Secondary

End point timeframe:

Patients were followed for a minimum of 2 years post registration

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Median PFS survival time (months)				
median (confidence interval 95%)	9.00 (6.77 to 12.74)			

Attachments (see zip file)	PFS.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival time

End point title	Overall Survival time

End point description:

Defined as the number of whole days between the date of registration until death from any cause. Patients who are alive at the end of the study will be censored at the date last know to be alive.

End point type	Secondary

End point timeframe:

Any time during the trial

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: median survival time (months)				
median (confidence interval 95%)	19.4 (13.2 to 24.7)			

Attachments (see zip file)	OS.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Duration

End point title	Treatment Duration

End point description:

Dose intensity is defined as the total dose of Pazopanib prescribed to each patients as a proportion of the planned protocol dose of 800mg per day for the 6 months during which time treatment tolerability was assessed.

End point type	Secondary

End point timeframe:

Within 6 months of registration

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Percentage				
median (inter-quartile range (Q1-Q3))	91.8 (72.2 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Number of whole days from the date complete or partial response is determined by RECIST to the date of progression determined by RECIST.

End point type	Secondary

End point timeframe:

Registration to end of follow up

End point values	Pazopanib			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
median (inter-quartile range (Q1-Q3))	7.5 (5.7 to 13.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Details of all AEs grade as CTCAE grade 3 or higher were documented and reported from the date signed consent was given until 30 days after the last administration of trial pazopanib.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Pazopanib

Reporting group description: -

Serious adverse events	Pazopanib		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 75 (65.33%)		
number of deaths (all causes)	58		
number of deaths resulting from adverse events	6		
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombotic event			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Pyrexia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	4 / 75 (5.33%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Laryngeal haemorrhage				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shortness of breath			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Emphysema			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sick sinus syndrome			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Presyncope			

subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attacks				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Pulmonary fibrosis				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	6 / 75 (8.00%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Anal haemorrhage				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea and vomiting			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Vomiting			
subjects affected / exposed	3 / 75 (4.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bileduct obstruction			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Hypothyroidism				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	5 / 75 (6.67%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 2			
Muscle weakness - lower limb				
subjects affected / exposed	2 / 75 (2.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pain - right leg				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchial infection				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest infection				
subjects affected / exposed	1 / 75 (1.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Infection				
subjects affected / exposed	3 / 75 (4.00%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			

Sepsis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 75 (2.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Pazopanib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 75 (88.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 75 (10.67%)		
occurrences (all)	9		

Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3		
Creatinine increased subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3		
GGT increased subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 7		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 7		
Serum amylase increased subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4		
Other investigations - not specified subjects affected / exposed occurrences (all)	18 / 75 (24.00%) 145		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	25 / 75 (33.33%) 117		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	9 / 75 (12.00%) 25		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	22 / 75 (29.33%) 32		
Pain subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 8		
Gastrointestinal disorders Abdominal pain			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5 4 / 75 (5.33%) 6 3 / 75 (4.00%) 3 4 / 75 (5.33%) 5 4 / 75 (5.33%) 4		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 5 / 75 (6.67%) 8		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 3 / 75 (4.00%) 6		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Muscle weakness - lower limb subjects affected / exposed occurrences (all)	 3 / 75 (4.00%) 4 7 / 75 (9.33%) 10 4 / 75 (5.33%) 5		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 3 / 75 (4.00%) 3		

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	10		
Hyperkalaemia			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Hypertriglyceridaemia			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	11		
Hypoalbuminaemia			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	8 / 75 (10.67%)		
occurrences (all)	11		
Hypophosphataemia			
subjects affected / exposed	8 / 75 (10.67%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2012	Updated definition of Efficacy primary outcome measure: Proportion of patients who are progression free and alive at 6 months.
22 May 2012	Screening Bone scan, CT scan Head and CT scan Chest/Abdomen/Pelvis allowed within 4 weeks of registration (previously within 2 weeks).
13 July 2012	Change in protocol version numbering from 1.3 to 4 without changes in content.
04 October 2012	Table on page 21 amended to specify that informed consent must be obtained within 4 weeks of registration rather than 2.
30 January 2013	Bone Scan, CT Scan Head, and CT scan Chest/Abdo/Pelvis allowed within 6 weeks of registration (previously within 4 weeks)
30 May 2013	Addition of serum liver test monitoring at week 3 (ALT, AST and total bilirubin). Bone scan and CT scan head now to be performed as clinically indicated (within 6 weeks prior to registration if being performed) rather than as mandatory at baseline. Clarification that assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated number of weeks prior to registration. Clarification that scans can be performed up to 5 days prior to the treatment week visit. Requirement for dynamic phase contrast enhanced CT scans removed, CT scans should be performed as per local practice.
04 December 2013	Term "Clinically relevant" changed to 'intolerable event' to avoid confusions. Slight change in the definition of the primary endpoint. The wording 'Adverse events which result in a decrease of the patient's performance status' has been removed from the definition of an 'intolerable event'. The wording 'lead to a drug discontinuation of greater than 3 weeks' has been added to the definition of an intolerable event. Addition to permitted concomitant medications to be used with caution w(PPIs, H2-H2-antagonists and antacids). Update to the End of trial definition: The end of trial will be at the point when all patients have a minimum of 12 months follow-up from registration or until death. Several typo corrections.
03 November 2016	Changes to trial personnel. Trial Office telephone number updated. Recruitment period extended until August 2016. References to Novartis changed to GSK. Change to drug supply to either clinical trial or commercial supply. Inclusion of a 3 day window for treatment visit dates. Change to scan schedule from 8 weekly for the duration of the trial to 12 weekly from week 52 onwards. Revised toxicity management relating to Liver toxicities (specific Treatment Emergent Hepatotoxicity can result in the patient having to be dose reduced to 400mg without having a step of 600mg). Blood sub-study removed. Amended definition of Adverse Events to reflect change in collection of abnormal laboratory values. Inclusion of updated TNM staging information

19 June 2017	Change to trial personnel and telephone contact number for urgent clinical queries. Definition of Tolerability changed from ratio to proportion of patients who are free from grade 3- grade 4 adverse events which are drug related and classified as an 'intolerable event'. References to primary and secondary endpoints changed to outcomes. Removal of reference to Trial Steering Committee (TSC) throughout. Amended trial duration: Change of follow up from 12 months after last dose of Pazopanib to until 31st December 2018 to allow for a minimum of 24 months follow up for all patients. Clarification that all patients will be followed up until end of trial follow up period. Amended End of trial definition to until all patients have been followed up until death or 31st December 2018, whichever is sooner (previously at the point when all patients have a minimum of 12 months follow up from registration or until death). Secondary outcomes analysis timepoint changed from when all patients have a minimum of 12 months follow up to when all patients have completed follow up.
12 February 2018	Change to form of commercially supplied study drug and clarification of IMP supply.
01 March 2019	Change of Chief Investigator. Change in Data Protection Regulations. Update to Trial Management team details.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported