Clinical trial results:
A Randomised Phase II study investigating pazopanib vs weekly paclitaxel in relapsed or progressive Transitional Cell Carcinoma (TCC) of the urothelium.

Summary

EudraCT number	2011-001841-34
Trial protocol	GB
Global end of trial date	06 July 2016

Results information

Result version number	v1 (current)
This version publication date	22 June 2018
First version publication date	22 June 2018

Trial information

Trial identification

Sponsor protocol code	PLUTO2011

Additional study identifiers

ISRCTN number	ISRCTN73030316
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow & Clyde
Sponsor organisation address	Gartnavel Royal Hospital, Glasgow, United Kingdom,
Public contact	Research & Development, NHS Greater Glasgow & Clyde, +44 01412111789, R&DIMP@ggc.scot.nhs.uk
Scientific contact	Research & Development, NHS Greater Glasgow & Clyde, +44 01412111789, R&DIMP@ggc.scot.nhs.uk
Sponsor organisation name	University of Glasgow
Sponsor organisation address	University Avenue, Glasgow, United Kingdom, G12 8QQ
Public contact	Ms Judith Dixon-Hughes, CRUK CTU Glasgow, 044 01413017540, judith.dixon@glasgow.ac.uk
Scientific contact	Professor Rob Jones, NHS Greater Glasgow and Clyde, r.jones@beatson.gla.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	19 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 July 2016
Global end of trial reached?	Yes
Global end of trial date	06 July 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to investigate whether pazopanib increases the overall survival time for patients with relapsed or progressive disease; in comparison to the current standard treatment, paclitaxel.

Protection of trial subjects:

As part of the study patients required to attend for additional clinic visits and investigations which would be above those considered to be standard care. The visit schedule and the number and type of investigations were fully explained to patients verbally and in writing via the patient information sheet to ensure patients were fully aware what was in entailed in participating in the trial prior to them consenting to the study.
The patient information sheet also fully explained the design of the study and that half of patients would receive paclitaxel and half would receive pazopanib.
The side effects of both treatments were explained in patient information sheet, as where the expected side effects for them. All patients were closely monitored throughout the course of the study for adverse events and were advised to report adverse events to their study team as they arose.

Background therapy: -

Evidence for comparator:

Although 2nd line chemotherapy is common practice in the UK and elsewhere, there is still no universally-accepted randomised controlled trial data to support the use of second-line chemotherapy rather than best supportive care alone and no international consensus on the optimal regimen. A survey of UK bladder cancer oncologists in 2009 showed that a wide variety of regimens were used in the 2nd line setting, none of which have supportive phase III data. Therefore, in order to better understand the likely benefits of pazopanib, a direct comparison of pazopanib and 'standard of care' is the ideal study to determine if pazopanib is worthy of further investigation in this setting. One suitable regimen is be weekly paclitaxel for up to 24 weeks. Unlike pazopanib, which can safely be given until disease progression or intolerance, paclitaxel may be associated with cumulative neurotoxicity, and so the total duration of therapy is limited in this study.

Actual start date of recruitment	01 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 131
Worldwide total number of subjects	131
EEA total number of subjects	131

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)	42
From 65 to 84 years	87
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was opened to recruitment in August 2010 and closed to recruitment in October 2014. This study was opened to recruitment in the UK only and recruited 131 patients.

Pre-assignment

Screening details:

Consent for the study could be taken up to 8 weeks prior to date of randomisation. All other screening evaluations were performed within 28 days of study entry

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - Paclitaxel

Arm description:

Patients will receive paclitaxel for up to 24 weeks. Infusions of paclitaxel 80mg/m2 will be administered on days 1, 8 and 25 of a 28 day cycle.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m2 day 1, 8, 15 of 28 day cycle for a maximum of 24 weeks

Arm title	Arm B - Pazopanib

Arm description:

Patients will receive pazopanib 800mg PO once daily until progression

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

Dosage and administration details:

800mg po daily until progression

Number of subjects in period 1	Arm A - Paclitaxel	Arm B - Pazopanib
Started	65	66
Completed	62	63
Not completed	3	3
Consent withdrawn by subject	3	2
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - Paclitaxel
Reporting group description:	
Patients will receive paclitaxel for up to 24 weeks. Infusions of paclitaxel 80mg/m2 will be administered on days 1, 8 and 25 of a 28 day cycle.	
Reporting group title	Arm B - Pazopanib
Reporting group description:	
Patients will receive pazopanib 800mg PO once daily until progression	

Reporting group values	Arm A - Paclitaxel	Arm B - Pazopanib	Total
Number of subjects	65	66	131
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age (years)			
Units: years			
median	70	69	
inter-quartile range (Q1-Q3)	63 to 77	61 to 75	-
Gender categorical			
Units: Subjects			
Female	16	22	38
Male	49	44	93
Response to previous treatment			
Response to previous treatment (time to progression: ≤ 6 months v > 6 months)			
Units: Subjects			
<= 6 months	49	48	97
>6 months	16	18	34
Presence of visceral and/or bone metastasis			
Presence of visceral and/or bone metastasis (yes/ no)			
Units: Subjects			
Yes	49	48	97
No	16	18	34
Patient ECOG performance status			
Patient ECOG performance status (0, 1, 2)			
Units: Subjects			
ECOG 0	25	26	51

ECOG 1	34	35	69
ECOG 2	6	5	11

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population includes all patients randomised onto the study.

Reporting group values	ITT		
Number of subjects	131		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age (years)			
Units: years			
median	69		
inter-quartile range (Q1-Q3)	62 to 77		
Gender categorical Units: Subjects			
Female	38		
Male	93		
Response to previous treatment			
Response to previous treatment (time to progression: ≤ 6 months v > 6 months)			
Units: Subjects			
<= 6 months	97		
>6 months	34		
Presence of visceral and/or bone metastasis			
Presence of visceral and/or bone metastasis (yes/ no)			
Units: Subjects			
Yes	97		
No	34		
Patient ECOG performance status			
Patient ECOG performance status (0, 1, 2)			
Units: Subjects			
ECOG 0	51		
ECOG 1	69		
ECOG 2	11		

End points

End points reporting groups

Reporting group title	Arm A - Paclitaxel
Reporting group description:	
Patients will receive paclitaxel for up to 24 weeks. Infusions of paclitaxel 80mg/m2 will be administered on days 1, 8 and 25 of a 28 day cycle.	
Reporting group title	Arm B - Pazopanib
Reporting group description:	
Patients will receive pazopanib 800mg PO once daily until progression	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intention-to-treat (ITT) population includes all patients randomised onto the study.	

Primary: Primary end point - Overall survival

End point title	Primary end point - Overall survival
End point description:	
End point type	Primary
End point timeframe:	
Overall survival is defined as the time from the date of randomisation to the date of death from any cause. Patients who do not die will be censored at the date they were last known to be alive.	

End point values	Arm A - Paclitaxel	Arm B - Pazopanib	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	65	66	131	
Units: Months				
median (confidence interval 80%)	8 (6.9 to 9.7)	4.7 (4.2 to 6.4)	6.7 (5.4 to 7.3)	

Statistical analyses

Statistical analysis title	Cox regression model
Statistical analysis description:	
The primary overall survival comparison was made using the estimated hazard ratio and p-values from a Cox regression model incorporating terms for the minimisation stratification factors and study arm.	
Comparison groups	Arm A - Paclitaxel v Arm B - Pazopanib
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.28

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.99
upper limit	1.67

Notes:

[1] - 1-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from start of treatment and throughout the study period and for at least 30 days after discontinuation of study medication. All adverse events were followed until resolution.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Arm A - Paclitaxel
Reporting group description: -	
Reporting group title	Arm B - Pazopanib

Reporting group description: -

Serious adverse events	Arm A - Paclitaxel	Arm B - Pazopanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 64 (51.56%)	42 / 65 (64.62%)	
number of deaths (all causes)	56	59	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures - Other, specify			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			

subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death NOS			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oedema limbs			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 64 (0.00%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	5 / 64 (7.81%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	2 / 6	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 64 (0.00%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular disorder			

subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal obstruction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 64 (9.38%)	5 / 65 (7.69%)	
occurrences causally related to treatment / all	3 / 7	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hoarseness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
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	3 / 64 (4.69%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders - Other, specify			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 64 (1.56%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 64 (0.00%)	6 / 65 (9.23%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alkaline phosphatase increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 64 (0.00%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine increased			
subjects affected / exposed	0 / 64 (0.00%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutrophil count decreased			
subjects affected / exposed	2 / 64 (3.13%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine output decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cognitive disturbance			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peripheral sensory neuropathy			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 64 (3.13%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 64 (1.56%)	6 / 65 (9.23%)	
occurrences causally related to treatment / all	0 / 1	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colonic obstruction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic perforation			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Constipation			
subjects affected / exposed	0 / 64 (0.00%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 64 (1.56%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 64 (3.13%)	5 / 65 (7.69%)	
occurrences causally related to treatment / all	3 / 3	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal fistula			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 64 (4.69%)	5 / 65 (7.69%)	
occurrences causally related to treatment / all	3 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Photosensitivity			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 64 (3.13%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chronic kidney disease			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 64 (4.69%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renam and urinary disorders - Other, specify			
subjects affected / exposed	1 / 64 (1.56%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary fistula			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	2 / 64 (3.13%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall pain			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness left-sided			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscle weakness upper limb			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bladder infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (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 - Other, specify			
subjects affected / exposed	5 / 64 (7.81%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	5 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection			
subjects affected / exposed	5 / 64 (7.81%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	6 / 64 (9.38%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	2 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 64 (3.13%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 64 (3.13%)	4 / 65 (6.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A - Paclitaxel	Arm B - Pazopanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 64 (89.06%)	62 / 65 (95.38%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 64 (7.81%)	16 / 65 (24.62%)	
occurrences (all)	15	38	
Hypotension			
subjects affected / exposed	4 / 64 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	7	0	
Thromboembolic event			
subjects affected / exposed	4 / 64 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	7	0	
General disorders and administration site conditions			
Oedema limbs			
subjects affected / exposed	8 / 64 (12.50%)	5 / 65 (7.69%)	
occurrences (all)	18	10	
General disorders and administration site conditions - Other, specify			
subjects affected / exposed	12 / 64 (18.75%)	9 / 65 (13.85%)	
occurrences (all)	37	18	
Pain			
subjects affected / exposed	21 / 64 (32.81%)	20 / 65 (30.77%)	
occurrences (all)	59	56	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	5 / 64 (7.81%)	0 / 65 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 64 (21.88%)	5 / 65 (7.69%)	
occurrences (all)	29	12	
Dyspnoea			
subjects affected / exposed	14 / 64 (21.88%)	10 / 65 (15.38%)	
occurrences (all)	27	30	
Epistaxis			

subjects affected / exposed	5 / 64 (7.81%)	0 / 65 (0.00%)	
occurrences (all)	6	0	
Hoarseness			
subjects affected / exposed	0 / 64 (0.00%)	4 / 65 (6.15%)	
occurrences (all)	0	23	
Respiratory, thoracic and mediastinal disorders - Other, specify			
subjects affected / exposed	9 / 64 (14.06%)	0 / 65 (0.00%)	
occurrences (all)	11	0	
Voice alteration			
subjects affected / exposed	0 / 64 (0.00%)	6 / 65 (9.23%)	
occurrences (all)	0	17	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 64 (7.81%)	4 / 65 (6.15%)	
occurrences (all)	11	12	
Investigations			
Weight loss			
subjects affected / exposed	0 / 64 (0.00%)	4 / 65 (6.15%)	
occurrences (all)	0	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 64 (0.00%)	5 / 65 (7.69%)	
occurrences (all)	0	12	
Dysgeusia			
subjects affected / exposed	4 / 64 (6.25%)	9 / 65 (13.85%)	
occurrences (all)	9	26	
Headache			
subjects affected / exposed	0 / 64 (0.00%)	4 / 65 (6.15%)	
occurrences (all)	0	10	
Peripheral motor neuropathy			
subjects affected / exposed	13 / 64 (20.31%)	0 / 65 (0.00%)	
occurrences (all)	24	0	
Peripheral sensory neuropathy			
subjects affected / exposed	28 / 64 (43.75%)	4 / 65 (6.15%)	
occurrences (all)	122	6	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 64 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	7	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 64 (18.75%)	8 / 65 (12.31%)	
occurrences (all)	20	14	
Constipation			
subjects affected / exposed	16 / 64 (25.00%)	14 / 65 (21.54%)	
occurrences (all)	43	36	
Diarrhoea			
subjects affected / exposed	18 / 64 (28.13%)	32 / 65 (49.23%)	
occurrences (all)	39	76	
Dry mouth			
subjects affected / exposed	4 / 64 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	5	0	
Dyspepsia			
subjects affected / exposed	6 / 64 (9.38%)	5 / 65 (7.69%)	
occurrences (all)	11	10	
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	6 / 64 (9.38%)	0 / 65 (0.00%)	
occurrences (all)	18	0	
Mucositis oral			
subjects affected / exposed	14 / 64 (21.88%)	11 / 65 (16.92%)	
occurrences (all)	26	24	
Nausea			
subjects affected / exposed	30 / 64 (46.88%)	31 / 65 (47.69%)	
occurrences (all)	70	81	
Vomiting			
subjects affected / exposed	17 / 64 (26.56%)	20 / 65 (30.77%)	
occurrences (all)	20	39	
Fatigue			
subjects affected / exposed	48 / 64 (75.00%)	49 / 65 (75.38%)	
occurrences (all)	190	184	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	28 / 64 (43.75%)	0 / 65 (0.00%)	
occurrences (all)	95	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 64 (0.00%)	8 / 65 (12.31%)	
occurrences (all)	0	18	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	13 / 64 (20.31%)	6 / 65 (9.23%)	
occurrences (all)	30	27	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	6 / 64 (9.38%)	6 / 65 (9.23%)	
occurrences (all)	10	9	
Renal and urinary disorders - Other, specify			
subjects affected / exposed	6 / 64 (9.38%)	9 / 65 (13.85%)	
occurrences (all)	14	14	
Urinary frequency			
subjects affected / exposed	4 / 64 (6.25%)	0 / 65 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 64 (12.50%)	9 / 65 (13.85%)	
occurrences (all)	16	19	
Musculoskeletal and connective tissue disorder - Other, specify			
subjects affected / exposed	5 / 64 (7.81%)	0 / 65 (0.00%)	
occurrences (all)	5	0	
Myalgia			
subjects affected / exposed	11 / 64 (17.19%)	5 / 65 (7.69%)	
occurrences (all)	23	7	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	8 / 64 (12.50%)	6 / 65 (9.23%)	
occurrences (all)	9	18	
Urinary tract infection			

subjects affected / exposed occurrences (all)	9 / 64 (14.06%) 13	7 / 65 (10.77%) 11	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	 15 / 64 (23.44%) 22	 23 / 65 (35.38%) 63	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2012	Amendment to ethics after notice of non acceptance from MHRA - This made it clear that after 2 weeks of no treatment that patient should be withdrawn from study treatment, it also amended the QTc prolongation management section
25 April 2013	This amendment allowed for a single additional liver function test for pazopanib patients. This reflected revised safety advice issued by the manufacturer. The eligibility criteria and dose modification criteria regarding liver function abnormalities have also been amended in line with this new advice. The eligibility criteria was also broadened to include patients with ECOG performance status 2. Also a negative urinalysis dipstick test has also been added as sufficient evidence of the absence of proteinuria.
04 August 2014	A restriction on the concomitant use of strong CYP3A4 inhibitors for patients receiving pazopanib was added in line with emerging data supplied by the manufacturer
22 October 2014	This amendment was to advise of a termporay halt to the trial on the advise of the IDMC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported